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THE WESTERN Journal of Medicine

VOLUME 124 • NUMBER 1 **JANUARY 1976**

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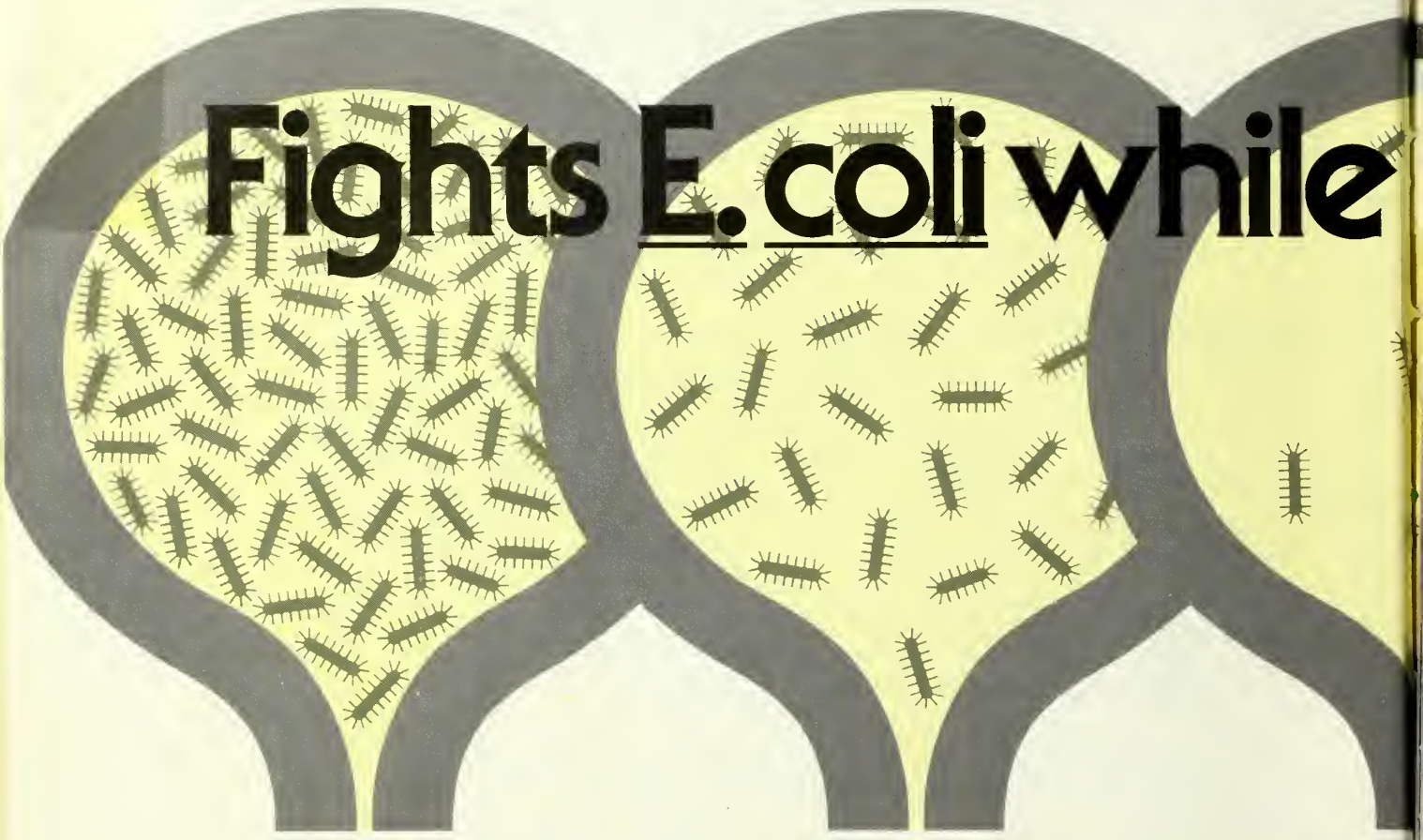

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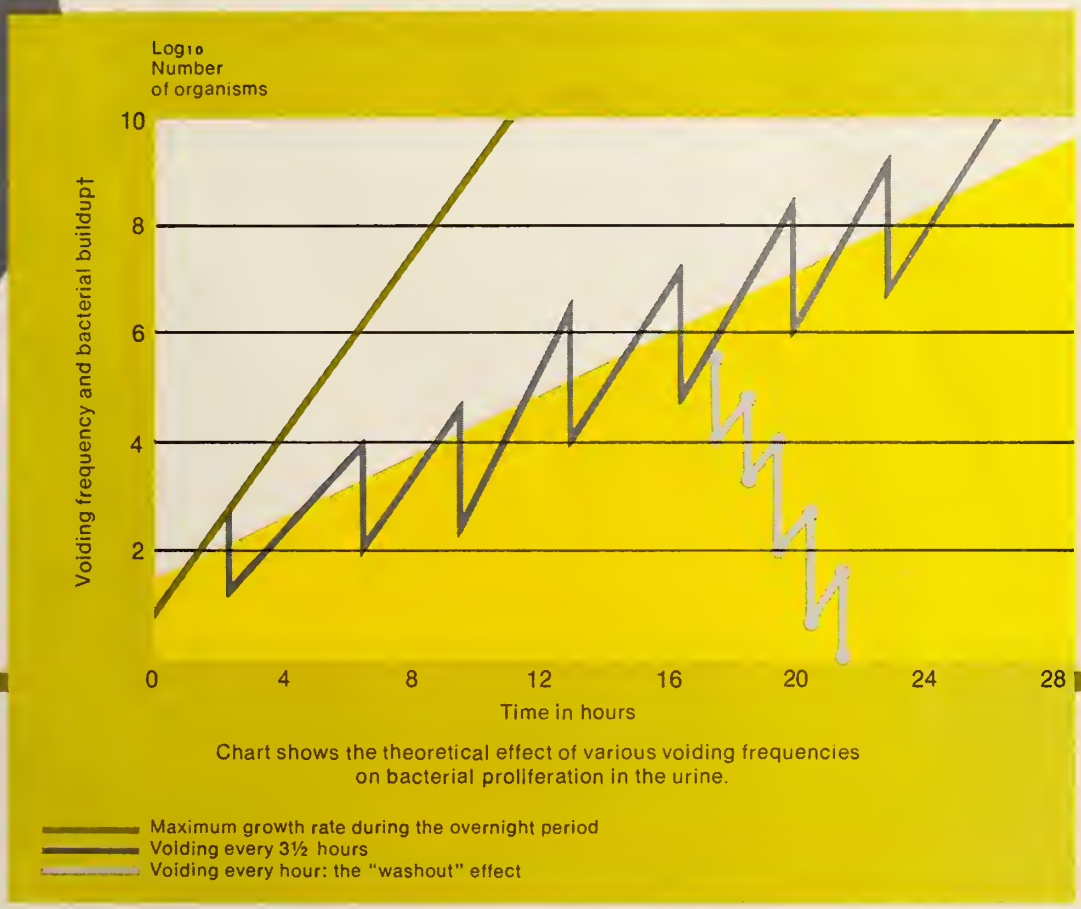

Chart shows the theoretical effect of various voiding frequencies on bacterial proliferation in the urine.

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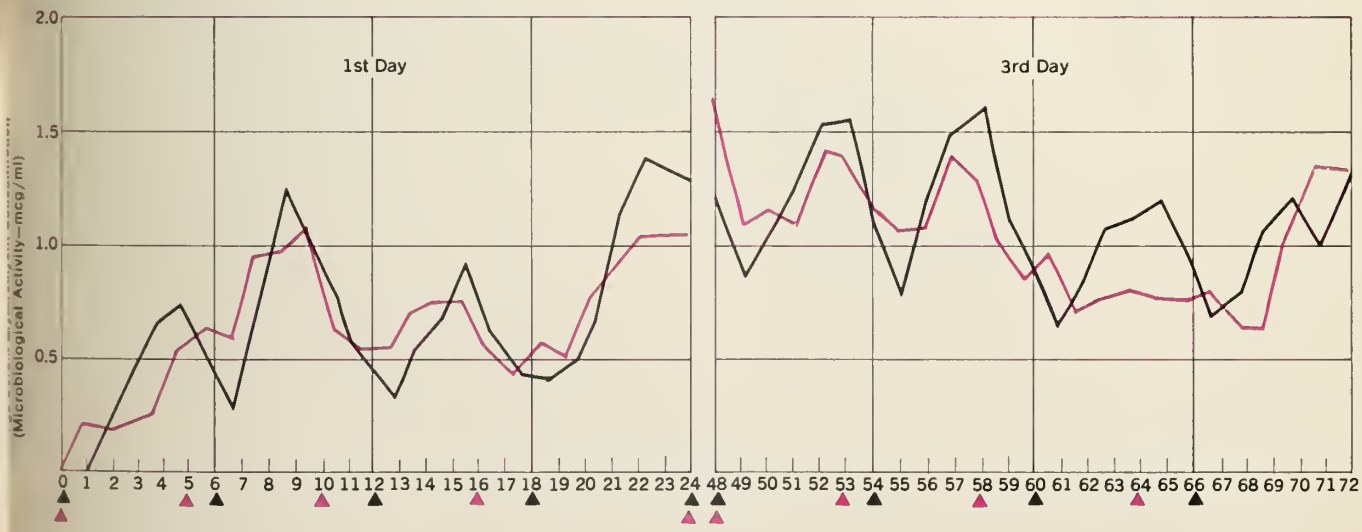

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

PRACTICAL PSYCHIATRY FOR THE PRIMARY PHYSICIAN—James R. Hodge, MD, Lecturer and Adjunct Professor, Department of Psychology, Akron University; Chief of Psychiatry section, Akron City Hospital; and Psychiatric Consultant, Veterans Administration Hospital. Nelson-Hall Publishers, 325 W. Jackson Blvd., Chicago (60606), 1975. 357 pages, $15.00

PRINCIPLES OF CLINICAL CARDIOLOGY—An Analytical Approach—Arthur Selzer, MD, Chief of Cardiology and Director of Cardiac Laboratories, Presbyterian Hospital of Pacific Medical Center, San Francisco; Clinical Professor of Medicine, University of California, San Francisco, and Stanford University School of Medicine. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1975. 735 pages, $18.50.

THE PSYCHOLOGY OF STRENGTH—Jon Alan Kangas, PhD, Clinical Psychologist and Director of the Testing and Counseling Center, University of Santa Clara; and George Freeman Solomon, MD, Clinical Professor of Psychiatry, UCLA School of Medicine, Director of Medical Education, Fresno County Department of Health, and Chief of Psychiatry, Valley Medical Center of Fresno. Prentice-Hall, Inc., Route 9W, Englewood Cliffs, NJ (07632), 1975. 182 pages, $2.95 (Paperback).

REVIEW OF MEDICAL PHYSIOLOGY—Seventh Edition—William F. Ganong, MD, Professor and Chairman, Department of Physiology, University of California, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1975. 587 pages, $10.50.

REVIEW OF PHYSIOLOGICAL CHEMISTRY—Fifteenth Edition—Harold A. Harper, PhD, Professor of Biochemistry, University of California, San Francisco; Biochemist Consultant to the Clinical Investigation Center, Naval Regional Medical Center, Oakland. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1975. 570 pages, $10.00.

THE SACCHARINE DISEASE—T. L. Cleave, MRCP(London), Surgeon-Captain Royal Navy (Retd.), Formerly Director of Medical Research, Institute of Naval Medicine. Keats Publishing, Inc., 36 Grove Street, P.O. Box 876, New Caanan, Conn. (06840), 1975. 200 pages, $7.95.

SUGGESTION OF THE DEVIL—The Origins of Madness—Judith S. Neaman, PhD. Anchor Press/Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1975. 240 pages, $2.50 (Paperback).

TALK BACK TO YOUR DOCTOR—How to Demand (and Recognize) High-Quality Health Care—Arthur Levin, MD. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1975. 245 pages, $7.95.

TEXTBOOK OF MEDICINE (Cecil-Loeb)—Fourteenth Edition—Edited by Paul B. Beeson, MD, Distinguished Physician, United States Veterans Administration, University of Washington School of Medicine; Formerly Nuffield Professor of Clinical Medicine, University of Oxford; and Walsh McDermott, MD, Professor of Public Affairs in Medicine, Cornell University Medical College, Attending Physician, the New York Hospital, with 200 Contributors. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1975. 1970 pages, 245 illustrations, Single Volume: $34.50, Two-Volume Set $40.00.

TRACTION AND ORTHOPAEDIC APPLIANCES—John D. M. Stewart, MA (Cantab), FRCS(England), Consultant Orthopaedic Surgeon, Chichester & Graylingwell, and Worthing, Southlands & District Groups of Hospitals. Longman Inc., 72 Fifth Avenue, New York City (10011), 1975. 206 pages, $19.00.

USES OF WINE IN MEDICAL PRACTICE—Ninth Edition—Wine Advisory Board, San Francisco. Wine Institute, 165 Post Street, San Francisco (94108), 1975. 72 pages, available, free of charge, to members of the medical profession.

YOUR SECOND LIFE—Harold L. Karpman, MD, Associate Clinical Professor, University of California, Los Angeles, School of Medicine, and Attending Physician, Cedars-Sinai Medical Center, Los Angeles; and Sam Locke, film and magazine writer. J. P. Tarcher, Inc., 9110 Sunset Blvd., Los Angeles (90069), 1975. 266 pages, $8.95.

PROBLEM-ORIENTED MEDICAL DIAGNOSIS—Editor: H. Harold Friedman, MD, Associate Clinical Professor of Medicine, University of Colorado School of Medicine, Attending Physician and Director, Heart Station, General Rose Memorial Hospital and Attending Physician, Saint Joseph Hospital, Denver; Consulting Editor: Solomon Papper, MD, Distinguished Professor of Medicine, University of Oklahoma College of Medicine, Distinguished Physician, Oklahoma City Veterans Administration Hospital. Little, Brown and Company, 34 Beacon Street, Boston (02106), 1975. 447 pages, $8.95.

RECENT ADVANCES IN PAEDIATRIC SURGERY—3rd Edition—Edited by Andrew W. Wilkinson, ChM(Edin) FRCS(Edin) FRCS(Eng), Nuffield Professor of Paediatric Surgery, Institute of Child Health, University of London; Consultant Surgeon, The Hospital for Sick Children, London. Longman Inc., Churchill Livingstone-Medical Division, 72 Fifth Avenue, New York City (10011), 1975. 220 pages, $24.50.

SCREENING IN GENERAL PRACTICE—Edited by C. R. Hart, MB, MRCGP, FRHist S, General Practitioner, Yaxley, Peterborough. Longman Inc., Churchill Livingstone—Medical Division, 72 Fifth Avenue, New York City (10011), 1975. 338 pages, $16.00.

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Indication: For the relief of mild to moderate pain, either alone or accompanied by fever.

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Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery The patient should be cautioned accordingly

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Usage in Children—Propoxyphene is not recommended for use in children, because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances

The chronic ingestion of propoxyphene in doses exceeding 800 mg per day has caused toxic psychoses and convulsions [011375]

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Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery The patient should be cautioned accordingly

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards

Usage in Children—Propoxyphene is not recommended for use in children because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group

Salicylates should be used with extreme caution in the presence of peptic ulcer or coagulation abnormalities.

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Salicylates may enhance the effect of anticoagulants and inhibit the uricosuric effect of uricosuric agents.

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Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg per day has caused toxic psychoses and convulsions. [011375]

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Opinion & Dialogue

Should a specially prepared package insert be made available to patients?

Dr. Alexander M. Schmidt
Commissioner,
Food and Drug
Administration

Dr. James H. Sammons
Executive Vice President
of the American
Medical Association

The idea of a so-called patient package insert has been around for a long time. Many physicians already use written instruction sheets to provide patients with information about the drugs they are taking. And some physicians give verbal instructions; but in too many instances these are what I call eye-glazing exercises. I have seen patients sit with glazed eyes listening to a rapid-fire lecture by a hurried physician who has 20 people out in his waiting room. These patients aren't given sufficient understanding and therefore do not follow instructions. So I think the idea of an official package insert for patients is a good one. Perhaps we should really think of this kind of information simply as an extension of drug labeling.

The benefits of patient involvement

Many physicians may not realize how frequently a patient obtains his drug information from Aunt Tillie or the next door neighbor. And this information is almost always bad or irrelevant to the case at hand. Furthermore, the incentive to go along with a prescribed program is slim if the only reading matter the patient receives, along with his prescription, is a bill.

As an educator I am impressed by the principle that the best way to get someone to do something is to involve him in the process. So the

I think there are advantages as well as some real disadvantages in a patient package insert. When you begin to use semi-medical or medical terms to describe complications or possible sequelae of disease or treatment, you may frighten the patient—particularly since the more highly sophisticated patient is not the one who is going to read the insert. The patient who will read it is the one most susceptible to fright and confusion by the language.

On the positive side, a package insert will probably give the patient better insight into why he is being treated the way he is, and it may give the physician a little bit more time. But it does not remove from the physician the need or obligation to explain the insert.

Some pitfalls in the inclusion of side effects

Certainly a patient should be warned of the possibility of serious side reactions—to know what the real dangers are. But it doesn't do a bit of good to indicate that a patient on oral penicillin may develop a rash, itching, or a drop in blood pressure. Or that he may faint. I think the real danger is that fright engendered by the insert may possibly outweigh the potential good.

main purpose of drug information for the patient is to get his cooperation in following a drug regimen.

Preparation and distribution of patient drug information

We would hope to amass information from physicians, medical societies, the pharmaceutical industry and centers of medical learning. The ultimate responsibility for uniform labeling must, however, rest with the Food and Drug Administration. There is nothing wrong with this agency saying, "this information is generally agreed upon and therefore it should be used," as long as our process for getting the information is sound.

Distribution of the information is a problem. In great measure it would depend on the medication in question. For example, in the case of an injectable long-acting progesterone, we would think it mandatory to issue two separate leaflets—a short one for the patient to read before getting the first shot and a long one to take home in order to make a decision about continuing therapy. In this case, the information might be put directly on the package and not removable at all. But for a medication like an antihistamine this information might be issued separately, thus giving the physician the option of distribution. This could preserve the placebo use, etc.

It is in the distribution of patient information that the pharmacist may get involved. As professionals and members of the health-care team and as a most important source of drug information to patients, pharmacists should be responsible for keeping medical and drug records on patients. It is also logical that they should distribute drug information to them.

Realistic problems must be considered

We have to expect that the introduction of an information device will also create new problems. First, how can we communicate complex and sophisticated information to people of widely divergent socioeconomic and ethnic groups? Second, what will we say? And third, how can we counteract the negative attitude of many physicians toward any outside influence or input? Hopefully the medical profession will respond by anticipating the problems and helping to solve them. Assuming we can also solve the difficulty of communicating information to diverse groups throughout the United States, our remaining task will be the inclusion of appropriate material.

What information is appropriate?

In my opinion, technical, chemical and such types of material should not be included. And there is no point in the routine listing of side effects like nausea and vomiting which seem to apply to practically all drugs, unless it is common with the drug. However, serious side effects should be listed, as should information about a medication that is potentially risky for other reasons.

Other pertinent information might consist of drug interactions, the need for laboratory follow-up, and special storage requirements. What we want to include is information that will help increase patient compliance with the therapy.

Positive aspects of patient drug information

Labeling medication for the patient would accomplish a number of good things: the patient could be on the lookout for possible serious side effects; his compliance would increase through greater understanding; the physician would be a better source of information since he would be freer to use his time more effectively; other members of the health-care team would benefit through patient understanding and cooperation; and, finally, the physician-patient relationship would probably be enhanced by the greater understanding on the part of the patient of what the physician is doing for him.

Only the doctor can remove that fear by 20 or 30 minutes of conversation.

I'm not suggesting that we withhold any information from the patient because, first of all, it would be totally dishonest and secondly, it would defeat the very purpose of the insert. I do think that a patient on the birth control pill should know about the incidence of phlebothrombosis.

If you're going to tell a patient the incidence of serious adverse reactions, then you have to tell him that a concerned medical decision was made to use a particular medication in his situation after careful consideration of the incidence of complications or side effects.

Emotionally unstable patients pose a special problem

There are patients who, because of severe emotional problems, could not handle the information contained in a patient package insert. Yet if we are going to have a package insert at all, we just can't have two inserts. I think we might simply have to tell the families of these patients to remove the insert from the package.

Legal implications of the patient package insert

Just what effect would a patient package insert have on malpractice? We could try to avoid any legal implications by pointing out that the physician has selected a particular medication because, in his professional judgment, it is the treatment of choice. For instance, you can't tell everyone taking antihistamines not to work just because a few patients develop extreme drowsiness which can lead to accidents. And what about the very small incidence of aplastic anemia rarely associated with chloramphenicol? If, based on sensitivity studies and other criteria, we decide to employ this particular antibiotic, we do so in full knowledge of this serious potential side effect. It's not a simple problem.

How do we handle an insert for medication used for a placebo effect?

With rare exceptions, physicians no longer use medications for a placebo effect. This question does raise the issue of how a patient may react to receiving a medication without a package insert.

Preparation of the package insert

The development of the insert ought to be a joint operation between physicians, the pharmaceutical industry, the A.M.A. and the F.D.A.

I view the A.M.A.'s role as a coordinator or catalyst. It is the only organization through which the profession as a whole, irrespective of specialty, can speak. It has relatively instant access to all the medical expertise in this country. And it can bring that professional expertise together to ensure a better package insert. The A.M.A. can work in conjunction with the industry that has produced the product and which is ultimately going to supply the insert.

I don't think we should rely, or expect to rely, on legislative committees and their nonprofessional staffs to make these decisions when it is perfectly within the power of the two groups to resolve the issues in the very best American tradition—without the government forcing us to do it. I think the F.D.A. has to be involved, but I'd like them to become involved because they were asked to become involved.

Pharmaceutical Manufacturers Association
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P·M·A

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(For full prescribing information, see package circular.)
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(Conjugated Estrogens Tablets, U.S.P.)

Indications: Based on a review of PREMARIN Tablets by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications for use as follows:
Effective: As replacement therapy for naturally occurring or surgically induced estrogen deficiency states associated with: the climacteric, including the menopausal syndrome and postmenopause; senile vaginitis and kraurosis vulvae, with or without pruritus.
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

Contraindications: Short acting estrogens are contraindicated in patients with (1) markedly impaired liver function; (2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal; (3) known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium; (4) thromboembolic disorders, thrombophlebitis, cerebral embolism, or in patients with a past history of these conditions; (5) undiagnosed abnormal genital bleeding.
Warnings: Estrogen therapy should not be given to women with recurrent chronic mastitis or abnormal mammograms except, if in the opinion of the physician, it is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen-dependent neoplasia.

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, estrogen therapy should be discontinued immediately.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Failure to control abnormal uterine bleeding or unexpected recurrence is an indication for curettage.
Precautions: As with all short acting estrogens, the following precautions should be observed:

A complete pretreatment physical examination should be performed with special reference to pelvic and breast examinations.

To avoid prolonged stimulation of the endometrium and breasts in climacteric or hypogonadal women, estrogens should be administered cyclically (3 week regimen with 1 week rest period—withdrawal bleeding may occur during rest period).

Because of individual variation in endogenous estrogen production, relative overdosage may occur which could cause undesirable effects such as abnormal or excessive uterine bleeding, mastodynia and edema.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

If unexplained or excessive vaginal bleeding should occur, reexamination should be made for organic pathology.

Pre-existing uterine fibromyomata may increase in size while using estrogens; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is incomplete.

Prolonged high dosages of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

Certain liver and endocrine function tests may be affected by exogenous estrogen administration. If test results are abnormal in a patient taking estrogen, they should be repeated after estrogen has been withdrawn for one cycle.
Adverse Reactions: The following adverse reactions have been reported associated with short acting estrogen administration:
nausea, vomiting, anorexia
gastrointestinal symptoms such as abdominal cramps and bloating
breakthrough bleeding, spotting, unusually heavy withdrawal bleeding (See DOSAGE AND ADMINISTRATION)
breast tenderness and enlargement
reactivation of endometriosis
possible diminution of lactation when given immediately postpartum
loss of libido and gynecomastia in males
edema
aggravation of migraine headaches
change in body weight (increase, decrease)
headache
allergic rash
hepatic cutaneous porphyria becoming manifest
Dosage and Administration: PREMARIN should be administered cyclically (3 weeks of daily estrogen and 1 week off) for all indications except selected cases of carcinoma and prevention of postpartum breast engorgement.

Menopausal Syndrome—1.25 mg. daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

If the patient has not menstruated within the last two months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding. If breakthrough bleeding (bleeding or spotting during estrogen therapy) occurs, increase estrogen dosage as needed to stop bleeding. In the following cycle, employ the dosage level used to stop breakthrough bleeding in the previous cycle. In subsequent cycles, the estrogen dosage is gradually reduced to the lowest level which will maintain the patient symptom-free.

Postmenopause—as a protective measure against estrogen deficiency-induced degenerative changes (*e.g.* osteoporosis, atrophic vaginitis, kraurosis vulvae)—0.3 mg. to 1.25 mg. daily and cyclically. Adjust dosage to lowest effective level.

Osteoporosis (to retard progression)—usual dosage 1.25 mg. daily and cyclically.

Senile Vaginitis, Kraurosis Vulvae with or without Pruritus—0.3 mg. to 1.25 mg. or more daily, depending upon the tissue response of the individual patient. Administer cyclically.
How Supplied: PREMARIN (Conjugated Estrogens Tablets, U.S.P.)

No. 865—Each *purple* tablet contains 2.5 mg., in bottles of 100 and 1,000.

No. 866—Each *yellow* tablet contains 1.25 mg., in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 867—Each *red* tablet contains 0.625 mg., in bottles of 100 and 1,000.

No. 868—Each *green* tablet contains 0.3 mg., in bottles of 100 and 1,000. 7352

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IN GONORRHEA

INJECTION

Wycillin®

(STERILE PROCAINE PENICILLIN G SUSPENSION) WYETH

In **Gonorrhea,** the drug regimen of choice is aqueous procaine penicillin G. In uncomplicated cases, administration of 4.8 million units together with 1 gram oral probenecid, given at least 30 minutes prior to injection, is recommended.

Indications: In treatment of moderately severe infections due to penicillin G-sensitive microorganisms sensitive to the low and persistent serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: When high sustained serum levels are required use aqueous penicillin G, IM or IV.

The following infection will usually respond to adequate dosages of intramuscular procaine penicillin G.—*N. gonorrhoeae:* acute and chronic (without bacteremia).

For deep intramuscular injection only.

Contraindication: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy.

Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Mental disturbances, including anxiety, confusion, agitation, depression, and hallucinations, have been reported in individuals following single-dose schedules for gonorrhea. Reactions have been transient, lasting from 15-30 minutes.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 cc. of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparations should not be used. Antihistaminics appear beneficial in treatment of procaine reaction.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy, discontinue penicillin and take appropriate measures.

If allergic reaction occurs, withdraw penicillin unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to penicillin therapy.

When treating gonococcal infections with suspected primary or secondary syphilis, perform proper diagnostic procedures, including darkfield examinations. In all cases in which concomitant syphilis is suspected, perform monthly serological tests for at least four months.

Adverse Reactions: (Penicillin has significant index of sensitization) skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; serum sickness-like reactions, including chills, fever, edema, arthralgia and prostration. Severe and often fatal anaphylaxis has been reported. (See "Warnings.")

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Dosage and Administration: Administer only by *deep intramuscular injection,* in upper outer quadrant of buttock. In infants and small children, midlateral aspect of thigh may be preferable. When doses are repeated, vary injection site. Before injection, aspirate to be sure needle bevel is not in blood vessel. If blood appears, remove needle and inject in another site.

Although some isolates of *Neisseria gonorrhoeae* have decreased susceptibility to penicillin, this resistance is relative, not absolute, and penicillin in large doses remains the drug of choice. Physicians are cautioned not to use less than recommended doses.

Gonorrheal infections (uncomplicated)—Men or Women: 4.8 million units intramuscularly divided into at least two doses and injected at different sites at one visit, together with 1 gram of oral probenecid, preferably given at least 30 minutes prior to injection.

NOTE: Treatment of severe complications of gonorrhea should be individualized using large amounts of short-acting penicillin. Gonorrheal endocarditis should be treated intensively with aqueous penicillin G. Prophylactic or epidemiologic treatment for gonorrhea (male and female) is accomplished with same treatment schedules as for uncomplicated gonorrhea.

Retreatment: The National Center for Disease Control, Venereal Disease Branch, U.S. Dept. H.E.W. recommends:

Test cure procedures at approximately 7-14 days after therapy. In the male, a gram-stained smear is adequate if positive; otherwise, a culture specimen should be obtained from the anterior urethra. In the female, culture specimens should be obtained from both the endocervical and anal canal sites.

Retreatment in males is indicated if urethral discharge persists 3 or more days following initial therapy and smear or culture remains positive. Follow-up treatment consists of 4.8 million units aqueous procaine penicillin G, I.M. divided in 2 injection sites at single visit.

In uncomplicated gonorrhea in the female, retreatment is indicated if follow-up cervical or rectal cultures remain positive for *N. gonorrhoeae.* Follow-up treatment consists of 4.8 million units aqueous procaine penicillin G daily on 2 successive days.

Syphilis: all gonorrhea patients should have a serologic test for syphilis at the time of diagnosis. Patients with gonorrhea who also have syphilis should be given additional treatment appropriate to the stage of syphilis.

Composition: Each disposable syringe 2,400,000 units (4-cc. size) contains procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer, and as w/v approximately 0.5% lecithin, 0.5% carboxymethylcellulose, 0.5% povidone, 0.1% methylparaben, and 0.01% propylparaben. The multiple-dose 10-cc. vial contains per cc. 300,000 units procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer and approximately 7 mg. lecithin, 2 mg. carboxymethylcellulose, 3 mg. povidone, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben, and 0.14 mg. propylparaben.

Five are graduating with honors. How many with VD?

On the average, you can figure the incidence of VD among teenagers at about 900 per 100,000 population.* And growing.

Among those in the 20-24 age-group, the incidence is even higher. And it, too, is growing.

In the long run, a populace educated to the risks and prevention of VD is probably the best answer to the problem. Meanwhile, though, adequate doses of the recommended types of penicillin remain a formidable weapon.

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INJECTION
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Syphilis is preferably treated with benzathine penicillin G, which is also the drug of choice for prophylaxis after exposure. Administration of 2.4 million units (1.2 million in each buttock) usually cures most cases of primary, secondary and latent syphilis with negative spinal fluid.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular benzathine penicillin G.—Venereal infections: Syphilis, yaws, beiel and pinta.

For deep intramuscular injection only.

Contraindication: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens.

Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms including fungi. Take appropriate measures should superinfection occur.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness-like reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high doses of parenteral penicillin.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Dosage and Administration: Venereal infections—

Syphilis—Primary, secondary and latent—2.4 million units (1 dose).

Late (tertiary and neurosyphilis)—2.4 million units at 7 day intervals for three doses.

Congenital—under 2 years of age, 50,000 units/Kg. body weight; ages 2-12 years, adjust dosage based on adult dosage schedule.

(Shake multiple-dose vial vigorously before withdrawing the desired dose.) Administer by **deep intramuscular injection** in the upper outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site. Before injecting the dose, aspirate to be sure needle bevel is not in a blood vessel. If blood appears, remove the needle and inject in another site.

Composition: Units benzathine penicillin G (as active ingredient): 2,400,000 units in 4-cc. single dose disposable syringe. Each disposable syringe also contains in aqueous suspension with sodium citrate buffer, as w/v approximately 0.5% lecithin, 0.6% carboxymethylcellulose, 0.6% povidone, 0.1% methylparaben, and 0.01% propylparaben. 300,000 units per cc.—10-cc. multi-dose vial. Each cc. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. povidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben, and 0.14 mg. propylparaben.

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THE WESTERN
Journal of Medicine

Neurosurgical Microvascular Bypass for Stroke

NORMAN CHATER, MD, *San Francisco,* and NORMAN PETERS, MD, *Houston*

A review of the present status of neurosurgical vascular bypass for problems of cerebrovascular occlusive disease is presented. In 70 patients who have undergone operations by one surgical team, the results are most encouraging in cases of transient ischemic attacks with hemodynamic lesions previously considered inoperable or inaccessible in the cerebral vasculature. The morbidity rate is acceptable and the present operative mortality rate is 1.4 percent.

Surgeons have made rapid and dramatic advances in the treatment of people with occlusive vascular diseases in the upper chest and neck. Perhaps we could encourage them to think of ways of going inside the head and modifying the circulation there, for at present even those individuals who have occlusive disease in the vertebral canal are not surgically approachable.

—H. G. WOLFF, MD, *Professor of Neurology, Princeton Conference on Cerebrovascular Disease, 1961*

IN THE PAST several years a number of papers have described the preliminary indications and early results of a neurosurgical microvascular bypass operation designed to increase the collateral blood supply in problems of occlusive cerebrovascular disease.[1-7] This surgical approach was originally developed by Yasargil and Donaghy eight years ago.[8,9] The symptoms in patients who met the criteria for surgical operation were felt to be due to hemodynamic insufficiency rather than embolic episodes. The surgical technique was described and, although the initial results were promising, a longer follow-up was required to observe the effect of microvascular bypass surgical procedures on the future clinical course of these patients. It also was felt necessary to evaluate (arteriographically, if possible) the patency rates of the surgical bypass postoperatively in a larger series of patients than those previously presented.[10]

This paper describes the results in 70 patients who have undergone a microvascular bypass neurosurgical procedure and who have been followed from 6 to 48 months postoperatively (see Table 1). Most patients in the group reported here were suffering from transient ischemic attacks (TIA) or had suffered a "completed stroke" with pronounced recovery and subsequent mild residual neurological deficit (Table 2). Arteriographic findings are shown in Table 3.

Stroke as a Clinical Problem

Stroke is the primary neurological health problem occurring in the nation today. Approximately 450,000 new strokes occur per year[11] of which 80 percent are due to cerebral vascular occlusive dis-

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ease.[12] In contrast, only 5 to 10 percent are due to subarachnoid hemorrhage, a major interest in the neurosurgical literature. It is estimated that 2 million people in America are presently disabled and unemployable as a result of stroke. The majority of such persons are under 65 years of age and are in the so-called "preretirement" or productive years.[13]

Cerebral Vascular Occlusive Disease and Arteriographic Findings

In patients in whom transient ischemic attacks have developed, there is a 13 to 60 percent chance of a completed stroke occurring within four years.[14-17] The outstanding aim of stroke therapy, therefore, is to prevent such a disaster and, if possible, to improve the quality of life.

A recent analysis of 123 consecutive patients presenting with transient ischemic symptoms at a university vascular clinic showed that 19 percent (N = 23) had a completely occluded internal carotid artery as the cause of the hemodynamic cerebrovascular insufficiency. In a short follow-up period three patients of the 23 suffered a completed stroke.[18]

In the National Cooperative Study, arteriographic investigation showed that 6 percent of the patients studied had purely inaccessible lesions in the cerebral vasculature.[19] An additional 16 percent of patients studied for cerebrovascular symptoms were shown to have old completed internal carotid occlusions, which, at present, are considered inoperable because of the low success rate of reopening the vessel.[20,21] Therefore, in 22 percent of patients studied by arteriography, "inoperable or inaccessible lesions" with present conventional surgical techniques may be present. This potentially amounts to approximately 15,000 persons per year presenting with transient ischemic attacks without permanent neurological deficit.

TABLE 1.—*Analysis of Bypass Status, January 1975*

Number of cases	70
Men	85%
Women	15%
Over 65, retirement years	25%
Under 65, working years	75%
Average age preretirement, most patients in late 50's	62 yrs
Minimum follow-up	6 mos
Average follow-up	16 mos

TABLE 2.—*Types of Clinical Presentation*

	Number	*Percent*
TIA or RIND	41	58
"Completed stroke"		
Mild	18	25
Moderate	3	5
Severe	5	7
Progressive stroke	3	5
TOTAL	70	

TIA = transient ischemic attack, neurological dysfunction under 24 hours with complete recovery
RIND = reversible ischemic neurological deficit, neurological dysfunction over 24 hours with complete recovery
Mild = clumsiness of hand or leg, fluctuating at times, fluctuating dysphasia
Moderate = hemiparesis or monoparesis, dysphasia nonfluctuating
Severe = hemiplegia, monoplegia, aphasia
Progressive = progressive loss of neurological function

TABLE 3.—*Arteriographic Findings*

	Number	*Percent*
BICO	11	16
ICO	25	35
SS	13	19
MOS	9	13
MCS	6	8
MCO	6	8
TOTAL	70	

BICO = bilateral internal carotid occlusion
ICO = internal carotid occlusion
SS = siphon stenosis (cavernous portion of carotid artery)
MOS = multiple vessel occlusions and stenoses (intra- or extracranial)
MCO = middle cerebral occlusion
MCS = middle cerebral stenosis

Theoretical Basis of the Surgical Procedure

Based on Baker's extensive research on cerebral vascular occlusive lesions (amount of atherosclerosis deposited equals blood pressure times radius of vessel), this surgical approach may bypass the major obstructive pathology (Premise No. 1)[22,23] and surgically supply an additional collateral blood supply to ischemic areas. Since "hemodynamic" cerebrovascular insufficiency symptoms are the result of insufficient collateral supply rather than the block itself (Premise No. 2)[24-27] such a surgical procedure may alleviate the symptoms and signs of cerebral ischemia. Whether such a surgical operation can partially or completely improve mild cerebrovascular neurological defects is still open to debate (Premise No. 3). Some pathological studies have suggested that minor neurological deficits could be improved at least theoretically with the restoration of normal perfusion pressures to the areas of marginal flow.[28,29] At present, however, there is no reliable clinical method of determining in advance which neurons are poorly functioning because of partial anoxia or which neurons are, in fact, dead.

Present Indications for Surgical Operation

Indications for the microvascular bypass procedure fall into two categories: lateralized low perfusion syndromes and generalized low perfusion syndromes.

Lateralized Low Perfusion Syndromes

The symptoms in this category depend on the vessel involved (usually middle cerebral artery) and the functional collateral supply available; may be transient, progressive or fluctuating.

The types of causes are several:

- Old internal carotid occlusions with poor collaterals.
- Carotid (inaccessible) stenosis with poor collaterals.
- Middle cerebral stenosis with poor collaterals (atherosclerotic or vasculitis).
- Middle cerebral occlusions with mild or moderate deficit and absent recanalization and poor collaterals.
- Vertebral basilar lesions with poor collaterals.[30]
- Inoperable giant intracranial aneurysms due to poor collaterals.[31]

Generalized Low Perfusion Syndromes

There is a smaller group of patients who suffer from a generalized ischemic cerebrovascular syndrome due to multiple large vessel occlusive disease. In these persons, symptoms such as dizziness; incoordination; blurred vision; syncope; dementia, and transient motor, speech or sensory deficits may be noted.

Two causes may be given in this category: multiple vessel occlusions and multiple vessel inaccessible stenoses.

Surgical Technique

On the basis of hemodynamic principles and the determination of the most suitable cortical artery, Yasargil's initial operative approach was modified. First, a wide-based "U" shaped temporal or occipital flap incorporating the donor vessels and overlying the angular gyrus is reflected. A 4 cm craniectomy is fashioned at a point 6 cm above the external auditory meatus. This operative technique consistently exposes the vessels around the angular gyrus. With the use of an operating microscope, bipolar coagulation and microsurgical techniques, the superficial temporal artery or occipital artery is dissected free from its subcutaneous bed. The arachnoid is then carefully opened around the cortical vessel of appropriate size. A 5 mm segment of this cortical artery is isolated between two small atraumatic clamps. The tip of the superficial temporal artery is freed of its adventitia and an end-to-side anastomosis is then carried out with 10-0 interrupted nylon sutures. The craniectomy opening is covered with a 4 cm plastic disc which has a slit opening for passage of the superficial temporal artery. When the scalp is finally replaced, care is taken not to compress the superficial temporal artery.

The primary morbidity risk stems from the technical requirement to clamp a portion of the recipient cortical artery for approximately 20 minutes in order to carry out a satisfactory anastomosis in a bloodless field. When minor neurological deficits do occur postoperatively, the vast majority tend to clear spontaneously, if the cortical branch occlusion time is 30 minutes or less. An experienced surgical team is therefore a necessity.

The temporal lobe tip vessels as recipient candidates for the bypass have been abandoned because of two failures in patency attributed to technical problems due to the minute size (less than 1 mm) of the available cortical artery in this location. The post-temporal-angular cortical artery complex above the ear has been used exclusively and in the past 90 cases (September 1975) no major difficulties have been encountered in finding a suitable recipient vessel of sufficient size even though a small, well-localized craniectomy was utilized.

Analysis of Results

In a significant percentage of patients suffering from transient ischemic attacks, there is symptomatic relief following the surgical bypass. Therefore the quality of their lives is improved (see Table 4).

At the Mayo Clinic, investigators have extensively followed a series of 200 patients suffering from definite transient ischemic attacks clinically. In the Mayo group the stroke occurrence rate after 16 months was 22 percent.[16] In our series to date (with a similar follow-up period) the stroke occurrence incidence is 7 percent including those patients who suffered a stroke in the distribution of a vessel not supplied by the bypass. The inci-

dence of stroke in the hemisphere supplied by the bypass is 3 percent at present. It may be that in the future bilateral "surgical arterial bypasses" should be pursued more aggressively in patients with multiple vessel disease. The improvement rate in progressive and mild completed strokes was 62 percent (see Table 4). This statistic, of course, must be viewed cautiously as the natural history of spontaneous improvement in completed strokes is quite variable.

TABLE 4.—*Results of Clinical Therapy to Date*

	Number	*Asymptomatic or Improved Percent*
TIA or RIND	41	83*
Progressive	3	100
"Completed stroke"		
Mild	18	55†
Moderate	3	33
Severe	5	0
TOTAL	70	

Average follow-up 16 months.
See Table 2 for definitions of other terms used.

*One transient ischemic attack or less postoperatively.
†Objective evidence of postoperative improvement in speech, writing and daily tasks.

TABLE 5.—*Complications*

	Number	*Percent*
Morbidity		
Transient speech difficulty all cleared (dysphasia)	5	7.0
Transient weakness all cleared	2	3.0
Permanent increase in deficit, moderate parietal lobe dysfunction	1	1.4
Wound infection superficial, no surgical operation required	1	1.4
Marginal scalp ischemia, no surgical operation required	5	7.0
Subdural hygroma, all evacuated uneventfully	3	4.0
*Mortality**		
Operative		
Under 7 days, stroke opposite side	1	1.4
Under 30 days, GI hemorrhage—acute bleeding from chronic duodenal ulcer with intestinal perforation; 23 days postoperatively	1	1.4

*As of November 1975, operations have been carried out in 102 patients with no further mortality.

TABLE 6.—*Patency Rates of Bypass Postoperatively*

		Percent
Doppler ultrasound auscultation over bypass	70/70	100
Apparently open	65/70	93
Postoperative arteriograms, total cases	50/70	70
Patent on arteriograms	47/50	94

Discussion

The only death occurring within the first week after surgical operation was a stroke involving the opposite hemisphere from an embolic clot to the opposite intracranial carotid artery. The other death, occurring within the first month of operation, from gastrointestinal hemorrhage, could probably be avoided now by vigorous antacid regimes in all patients since they are usually placed on aspirin for one month postoperatively to aid in avoiding platelet clumping at the fresh bypass anastomotic sites (see Table 5). Patency rates of bypass postoperatively are shown in Table 6.

Objective evaluation of the effects of any new operation may be difficult to obtain. The ultimate test of whether this particular operative approach is useful clinically will be a comparison between similar groups of patients (operated versus non-operated) suffering from angiographically-shown inaccessible or inoperable cerebrovascular stenotic or occlusive lesions. In this age of "consumerism" and the patient's "bill of rights" there is some doubt that a reliable double blind randomized study can be implemented in this country. This is particularly true in states (such as California) where the emphasis on informed consent including discussion of the "alternatives of treatment" have such widespread implications in malpractice litigation.[32]

Several investigators have reported significant improvement in regional cerebral blood flow following such a bypass (allowing for the intrinsic errors implicit in the methods employed).[6,33,34] Other workers have documented a significant increase in retinal artery perfusion pressures following bypass for symptomatic internal carotid occlusions.[35]

These results, therefore, must continue to be considered preliminary in nature but in comparison to the available statistics on the natural history of cerebral vascular occlusive disease, surgeons involved in this aspect of neurosurgical therapy remain encouraged.

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Refer to: Reid KJ, Sakati N, Prichard LL, et al: Genetic counseling—An evaluation of public health genetic clinics. West J Med 124:6-12, Jan 1976

Genetic Counseling

An Evaluation of Public Health Genetic Clinics

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The geographic distribution of County Health Department clinic facilities in the state of California has made it readily possible to establish a regionalized program for genetic counseling services, using public health nurses as a major source of case-finding. From both consumer and health professional standpoints, regionalized satellite genetic counseling clinics have been successful, and in particular, the effectiveness of public health nurses in identifying clinical genetic problems is readily apparent.

Long-term follow-up reinforcement of genetic counseling appears to be an important conclusion from these studies. It is our suggestion that reinforcement of counseling would best be accomplished through the health team member (physician, nurse and so forth) following the patient or family rather than through the consulting geneticist.

GENETIC SERVICES, especially genetic counseling, are adaptable to implementation in ways that need not comply with the standard medical center concept of a hospital clinic to which all patients are channeled by a variety of referral mechanisms. Moreover, genetic services can be quite variable. They may require the sophisticated techniques available in a major medical center. On the other hand, most genetic counseling problems can be handled explicitly if the diagnosis is already established. All that is really needed for a genetic counselor is a place to talk and the ability to communicate.

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At our Genetics Clinic at mid-city University Hospital, affiliated with the University of California, San Diego School of Medicine, we were impressed with the degree of attrition in referrals for genetic services through departmental subspecialty clinics. Also, it appeared that patients seen in the medical center clinics represented only a fraction of families with genetic problems living in the community. Many families who might want or need genetic services presumably were not aware of their availability or, because of the mid-city location of University Hospital, found it difficult to reach the source of these services.

This report reflects the initial results from an 18-month effort, started in 1970 and still continuing, to (1) extend genetic services beyond the usual confines of a major medical center, (2) ascertain the response of families to these services and (3) learn the potential of other health professionals in helping to deliver genetic health care services.

In California there exists an excellent Department of Public Health with regional Public Health Centers located throughout each county. These clinics are staffed by public health nurses and physicians responsible for a variety of health care services, such as immunization, well-baby care, and pediatric and prenatal care. We elected to use this matrix for the delivery of genetic services in San Diego County which, with seven regional health centers, serves a population of 800,000 persons.

Health care is continuous through this health center system, with the nursing staff of each center in contact with families in the regional areas.

TABLE 1.—*Patients Seen at Public Health Center Genetics Clinic*

Clinical Problem	*Follow-up for Families*	
	Available	*Not Available*
Abortions, multiple spontaneous	2	2
Albinism, cutaneous	1	..
Albinism, tyrosinase negative	1	..
Anhidrotic ectodermal dysplasia	1	..
Apert's syndrome	2	..
Arterio-venous malformation	1	..
Beckwith's syndrome	..	1
Biliary atresia	1	..
Cataracts and nystagmus	1	..
Cataracts, bilateral, polar	1	..
Cataracts, congenital	..	2
Celiac disease	1	..
Cerebral palsy	4	..
Circulatory abnormalities, possible	..	1
Cleft lip and palate	4	3
Club foot	4	1
Club foot, congenital hip defect and urethral stricture	1	..
Corneal dystrophy, lattice-type	1	..
Craniosynostosis	2	..
Cystic fibrosis	3	..
Delayed development, etiology unknown	1	1
Diabetes mellitus	8	..
Down's syndrome	17	6
Drug use	..	2
Dubin-Johnson syndrome	..	1
Duchenne muscular dystrophy	2	4
Ear deformity	1	..
Epilepsy	2	..
Facio-scapulo-humeral muscular dystrophy	2	..
Familial pulmonary emphysema	2	..
Familial tremor	..	1
Friedrich's ataxia	1	..
Galactosemia	..	1
Glaucoma, congenital	1	..
Hand, congenital absence	1	..
Heart disease, congenital	1	..
Hemophilia, factor VIII deficiency	1	..
Hip, bilateral dislocation	2	..
Hip, dislocation	..	1
Holt-Oram syndrome	1	..
Homocystinuria	1	..
Huntington's chorea	2	2
Hydranencephaly	..	1
Hydrocephalus	..	1
Hyperlipoproteinemia, type IV	3	..
Hypothyroidism	..	1
Imperforate anus	1	1
Intussusception	..	1
Klippel-Trenaunay-Weber syndrome	1	..
Marfan's syndrome	3	..
Meningomyelocele with hydrocephaly	1	..
Mental retardation, etiology unknown	4	2
Mental retardation from cerebral hemorrhage	..	1
Microcephaly	2	..
Microcephaly and pulmonary vascular hypoplasia	..	1
Microphthalmia	1	..
Multiple congenital anomalies	2	4
Myasthenia gravis and Down's syndrome	1	..
Myelomeningocele	..	1
Narcolepsy	..	1
Nerve deafness	..	3
Nerve deafness, bilateral	1	..
Nerve deafness, cleft lip and palate	1	..
Neurofibromatosis	..	1
Nystagmus	1	..
Ocular albinism	..	1
Oculomotor apraxia	1	..
Osteodysplasty	1	..
Osteogenesis imperfecta	4	..
Penis, congenital absence	..	1
Pescaves, familial	1	..
Phenylketonuria	1	..
Phocomelia	1	1
Phocomelia and hemophilia	1	..
Pierre-Robin syndrome	2	..
Pyloric stenosis and anencephaly	1	..
Recto-vaginal fistula	1	..
Retinal detachment	1	..
Retinitis pigmentosa	3	..
Retinoblastoma	2	..
Rh incompatibility	..	3
Rh incompatibility and respiratory distress syndrome	1	..
Schizophrenia	1	..
Short stature	..	2
Sickle cell anemia or trait	9	8
Spielmeyer-Vogt disease	1	..
Strabismus, familial	1	..
Subdural hematoma	..	1
Sudden infant death	..	1
Syndactyly, bilateral	2	..
Thalassemia minor	..	1
Tracheo-esophageal fistula	1	..
Treacher Collins syndrome	2	..
Turner's syndrome	1	1
Urethral atresia	3	..
Urticaria pigmentosa	..	1
Vesico-ureteral reflux	..	1
Vitiligo	1	..
von Willebrand's disease	1	..
Wilm's tumor	1	..

Our interest in coordinating genetic services with the health centers provided a two-way opportunity: (1) patients would have a readily accessible route for referral for genetic services and (2) interaction between genetic health care specialists and public health nurses would provide the opportunity for increasing the skills of the nursing staff in recognizing genetic diseases and participating in genetic counseling.

Outline of the Program

The clinics were conducted in rotation at each of the seven health centers two half-days each week. The nursing staff of each clinic received 20 to 24 hours of didactic instruction in genetics including mendelian, X-linked and empiric risks with multifactorial inheritance mechanisms and chromosomal abnormalities. We established no rigid guidelines for the nursing staff to follow as to who might have a genetic problem and who might not. They were encouraged to refer any patient or family they felt might have a genetic problem or who expressed interest in genetic counseling. Both the nurses and the referring physician involved with any patient or family received a written summary of the genetic evaluation and counseling.

The referring public health nurse participated in the genetic counseling session with the attending staff at each clinic visit. At the end of each clinic day, the attending physician-counselor conducted a genetics seminar with the entire nursing staff, either using the case of a patient seen in that particular clinic or discussing a particular genetic entity to emphasize specific disciplines in genetics and counseling and to broaden the nurses' overall understanding of genetic disorders.

During the period of this report (18 months), 232 patients or family units were referred for diagnosis and counseling. A 47-part questionnaire was sent to each family and of the 232 families to whom we sent questionnaires, 70 could not be reached by mail (left original location with no forwarding address) or by phone. In part, this probably reflects the relatively transient population in parts of California. Of the 162 families contacted, 144 (89 percent) returned a completed questionnaire. Table 1 shows the various diagnoses for which the families were seen. The subsequent data in this report are related to the 144 patients who submitted completed questionnaires. Comparison of data in Table 1 shows a reasonable degree of similarity between the medical problems encountered in the group unavailable for follow-up and the group which was contacted for follow-up.

From the total number (144) of responding families seen at the health centers, we found that approximately 50 percent could be counseled without further study based upon a well-established diagnosis confirmed by our obtaining the patient's medical records. The remaining approximately 50 percent required further evaluation for diagnosis before counseling. This further evaluation was usually obtained by specific laboratory tests on referral to various clinics and laboratories at University Hospital.

Results

Source of Referral to the Genetics Clinic

Of the referrals, 75 percent were made directly through the nursing staff at the health centers. Communication with the 15 families referred by themselves or friends showed that this occurred through family knowledge of public health nurse referral of other families. Therefore, the total direct and indirect influence of public health nurses in genetic referral in this group of 144 families is greater than 85 percent.

Parental Age, Family Size and Income

As anticipated, more than 85 percent of the patients or parents of defective children seen were between the ages of 20 and 40. Most families seen had from 1 to 4 children with a median number for all 144 families of 2.3 children. There were almost twice as many families in the $5,000 to $10,000 annual income bracket as in each of the income groups below or above these amounts. Only 25 percent of the families had an income of greater than $10,000 annually.

Subjective Reasons for Attending the Genetics Clinic

Although 85 percent of the patients were referred by public health nurses, only 14 percent of the respondents considered recommendation by a health nurse to be their only reason for going to the clinic. In contrast, nearly 75 percent felt their reason for attending the genetics clinic was concern for their possible future children or the risk that a genetic defect might affect their children's children or both.

Subjective Response to Genetic Services

A large proportion of the families seen (73 percent) felt they had no other or were aware of

no other resource for genetic services other than the newly established health center genetics clinics, and 94 percent of the families would or had already recommended the clinic to others. Approximately the same number (88 percent) felt that a regionally located genetics clinic greatly facilitated their use of these services. Approximately two thirds of the respondents felt they understood their or their child's problem better after counseling, but only one third felt they had learned where to get additional help for a defective child. Most families expressed a feeling that nurses and physicians were interested not only in the genetic problem but in them as persons. At the same time, most expressed the feeling that more follow-up visits to the genetics clinic would have been helpful.

Previous Counseling

Of the 144 families seen, 75 percent had not been counseled previously. Of the 25 percent of families counseled previously, 60 percent were counseled by their family physician and 30 percent by a "specialist." Only 10 percent indicated previously being counseled by a geneticist. Of 36 families (25 percent of the total) who received genetic counseling before being seen in the health center genetics clinic, only 20 percent felt they had understood previous counseling to any degree.

Subjective Interpretation of Genetic Risks

Table 2 depicts the genetic risks as provided by the counselor and the numerical recurrence risk as remembered by the patient. Earlier we mentioned that approximately 85 percent of clinic referrals were by public health nurses who had no significant background in genetics. As seen in Table 2, more than 75 percent of the families seen were obviously felt to have genetic problems by the counselor. Comparison of the data in Table 2 shows a reasonable agreement between recurrence risks given by the counselor and the numerical figure remembered by the patient.

Of considerable interest is the patient's interpretation of genetic risks. The subjects were asked to interpret their risks as high, moderate, low and zero. This information was then objectively cross-related to specific numerical recurrence risks as given by the counselor and as remembered by the patient. It should be stated parenthetically that we chose to consider autosomal recessive, autosomal dominant and X-linked categories as "high risk." Multifactorial inheritance and recurrence risk for chromosomal abnormalities were considered to be "moderate" or "low risk." There were 18 persons who did not respond to this portion of the questionnaire (12.5 percent).

In Table 3, we see the response of families/patients who considered their genetic risk for recurrence of a particular abnormality to be high. There were two patients who were told that the recurrence risk was zero and who remembered a zero risk yet considered this a high risk. Also, there were patients who were told zero risk but remembered 25, 50 and 100 percent risks—and correctly considered these high. Of the 55 patients in this group (Table 3), approximately 15 percent considered a 1 to 5 percent risk high. It

TABLE 2.—*Patient Recollection of Counseled Genetic Risks*

Value (Percent)	*Frequency Risk Given in Counseling*		*Frequency Risk Remembered by Patient*	
	Absolute	*Relative (Percent)*	*Absolute*	*Relative (Percent)*
Zero	34	23.5	41	28.5
1-5	47	32.6	42	29.2
5-10	1	0.8	2	1.3
25	30	20.8	29	20.1
50	24	16.7	22	15.3
X-linked	5	3.5	5	3.5
100	..	..	3	2.1
Not given	3	2.1	..	..
TOTALS	144	100.0	144	100.0

TABLE 3.—*Patient Interpretation of High Genetic Risk*

Recurrence Risk Given to Patient by Counselor (Percent)	*Specific Recurrent Risk Remembered by Patient (Percent)*							
	Zero	*1-5*	*5-10*	*25*	*50*	*X-linked*	*100*	*Totals*
Zero	2	0	0	1	1	0	1	5
1-5	2	8	1	1	1	0	0	13
25	0	0	0	14	1	0	2	17
50	1	0	0	3	11	0	0	15
X-linked	0	0	0	0	0	4	0	4

TABLE 4—*Patient Interpretation of Moderate Genetic Risk*

Recurrence Risk Given to Patient by Counselor (Percent)	*Specific Recurrent Risk Remembered by Patient (Percent)*							
	Zero	*1-5*	*5-10*	*25*	*50*	*X-linked*	*100*	*Totals*
Zero	1	0	0	0	0	0	0	1
1-5	0	4	0	0	0	0	0	4
5-10	0	0	1	0	0	0	0	1
25	0	0	0	5	0	0	0	5
50	0	0	0	0	2	0	0	2
X-linked	0	0	0	0	0	1	0	1

TABLE 5.—*Patient Interpretation of Low Genetic Risk*

Recurrence Risk Given to Patient by Counselor (Percent)	*Specific Recurrence Risk Remembered by Patient (Percent)*			
	Zero	*1-5*	*25*	*Totals*
Zero	7	1	0	8
1-5	2	14	3	19
25	0	2	1	3
50	0	0	0	0

TABLE 6.—*Patient Interpretation of No Genetic Risk*

Recurrence Risk Given to Patient by Counselor (Percent)	*Specific Recurrence Risk Remembered by Patient (Percent)*			
	Zero	*1-5*	*25*	*Totals*
Zero	15	0	0	15
1-5	3	3	0	6
25	1	0	0	1
50	1	1	1	3

TABLE 7.—*Influence of Genetic Counseling on Subsequent Pregnancies*

	Absolute Frequency	*Relative Frequency (Percent)*
No influence	64	44.4
Felt reassured	30	20.8
No more children	29	20.1
Plan to adopt	7	4.9
No decision	14	9.8
TOTALS	144	100.0

should be pointed out that young mothers who had children with 21 trisomy (Down's syndrome) in general were counseled that the recurrence risk was approximately 1 percent. The eight parents of children with Down's syndrome all correctly remembered a 1 percent recurrence risk but considered this high, and this accounts for virtually all of the families who considered a 1 to 5 percent risk high.

As shown in Table 3 and throughout the entire study, there is a consistently excellent understanding of recurrence risks in X-linked abnormalities. Thus the family's interpretation of high or low recurrence risks for X-linked disorders was based on whether they considered the X-linked defect to be severely destructive or not.

Approximately 53 percent of the families described in Table 3 were told recurrence risks that were high (25 percent, 50 percent and X-linked), remembered the numerical advice correctly, and considered the risks high. At least 20 percent of the respondents in Table 3 remained confused either about the numerical recurrence risk or the significance of the recurrence risks. Of particular concern are the three families who were given zero or 25 percent risk, yet remembered 100 percent risk, and the one patient who was given a 50 percent recurrence risk but remembered a zero risk although considering that risk high. What seems clear is that for this group of patients, counseling has not been ideal and confusion remains for a significant number of families.

Tables 4 and 5 summarize results from patients who considered their genetic risks either moderate or low. It is important to note that eight families (Table 4) who were counseled that the genetic risk was high (autosomal recessive, 5; dominant, 2; X-linked, 1) and understood the recurrence risk by its correct numerical value still considered the risk to be only moderate.

The patient interpretation of a small genetic risk (Table 5) seems to be well-correlated with the numerical understanding of each risk. Three patients were advised of a 1 to 5 percent recurrence risk, remembered a 25 percent risk but interpreted the risk as being small.

In Table 6 we see that 40 percent of the subjects who interpreted their genetic risks as zero were either counseled differently by the physician-geneticist or correctly remembered the numerical risk but incorrectly interpreted this as no risk. Although a low recurrence risk may be considered as no risk at all by the patient, depending upon the nature of the genetic variation, results depicted in Table 6 again indicate that genetic counseling may not have been adequate in this group of subjects.

Of respondents who were seen in only one counseling session, 26 percent incorrectly recalled recurrence risks as given by the counselor. Of the patients seen on two or more clinic visits, approximately 18 percent had inaccurate recall of recurrence risks. Therefore it would seem that improvement is needed in follow-up counseling and that, in most instances, more than a single genetic counseling session is required. From other data not reported here, patients and families express a strong opinion that more than one counseling session is highly desirable.

Influence of Genetic Counseling on Family Planning

As shown in Table 7, approximately 45 percent of the families seen have been influenced in family planning after counseling (either reassured about risks, plan to adopt or have no additional children), and an approximately equal number felt no influence at all on their plans for more

children. Of the families who decided not to have additional children following genetic counseling (20.1 percent), 65 percent are following some method of contraception and 36 percent have had some form of sterilization. In the main, families who felt no influence by genetic counseling on their family planning had already decided to have no more children before counseling. There were a few families who planned more children in the face of high genetic risks. These decisions were made largely because of religious beliefs.

Outcome of Subsequent Pregnancies

Thirty-four pregnancies have occurred subsequent to genetic counseling. Fifteen were planned and resulted in normal children. Seventeen were unplanned but also resulted in normal children. Two pregnancies resulted in defective children. In one unplanned pregnancy, a child was born with cleft lip and palate. The only previous pregnancy for this couple produced a child who, during infancy, had skin lesions characteristic of chloasma. The couple had been advised that these skin lesions were considered to be nongenetic. There was no family history of cleft lip or palate.

In a second family, a planned pregnancy resulted in a premature infant with respiratory distress syndrome and erythroblastosis fetalis. The infant died three weeks after birth. According to the results of the genetic counseling questionnaire submitted by these parents, they were aware of the Rh factor incompatibility and the genetic risks, but after counseling they had felt their risks were zero.

Discussion

The difficulty in interpreting studies to evaluate genetic counseling results mostly from the fact that currently no criteria or standards exist for this kind of evaluation. Although several excellent reports on the subject of counseling[1-12] have appeared recently, all suffer from the same deficiency and, like this report, use experiences unique to their particular program. The problem of this lack of standardization becomes particularly acute with the increasing number of genetic counseling services available and the interest of medical students, as well as established health professionals, in genetic counseling as part of their career plans. This is also relevant to the increasing number of master's degree programs for training in genetic counseling. There can be no question that criteria are needed upon which genetic counseling effectiveness can be ascertained.

Our studies are not intended to answer any of these dilemmas and may well provide information useful only to our own genetic counseling program. On the other hand, several general comments can be made.

There is no question that as a part of total medical care, genetic counseling clinics have more mobility and flexibility than other subspecialty services. A number of major medical centers have conducted regionalized genetic counseling clinics for several years (for example, Thomas Jefferson University;[10] the University of Colorado Medical Center;[11] the University of California, San Francisco Medical Center[12]). These programs are successful to the extent that services are provided to a patient population who might otherwise find it difficult to obtain access to genetic services. Patient response is overwhelmingly positive to regional clinics for genetic counseling.

The results in this report clearly show that with minimal training, health professionals without previous experience in genetic disease can readily learn to identify patients or families who might have a genetic disorder. Consequently, the referral mechanism for genetic counseling could attain a broader base without disturbing the primary physician-patient relationship. The results also show that regionalization of genetic clinics and utilization of public health nurses to identify genetic problems in families increases the effectiveness of consumer exposure to genetic counseling. Moreover, participation by public health nurses in genetic counseling services assures optimal opportunity for proper follow-up and reinforcement of counseling advice.

Ascertaining the effectiveness of genetic counseling is considerably more difficult. The results reported here confirm the finding of Leonard and co-workers[3] that the impact of a particular genetic disorder usually outweighs the numerical recurrence risks for many parents. For example, half of the families told that the recurrence risk for 21 trisomy was approximately 1 percent considered this to be a high risk. One might argue that simply telling a family that a recurrence risk exists might in some instances provide effective counseling.

Approximately 54 percent of the families who interpreted their counseling as a high recurrence risk were actually given such figures by the counselor and correctly remembered the numerical

risk. Our results show precise and complete understanding of genetic counseling for 36 percent of subjects in the moderate risk category, 53 percent in the low risk category and 60 percent in the no risk category. Thus the overall average for precise and complete understanding is 50 percent. However, out of 144 respondents in this study, 18 did not respond to this portion of the questionnaire. If one concludes that a large portion of those 18 respondents did not have the correct interpretation or understanding of their counseling, then the positive correlation between what the genetic counselor told the subject and what was interpreted by the subject could be close to 48 percent. If one interprets these results as at least one measurement of effectiveness, then it means that no better than half of the families in this study had completely effective counseling as far as understanding is concerned.

Approximately two thirds of the respondents (Table 7) felt that genetic counseling influenced plans for subsequent pregnancies. One might also argue that two thirds (those who were not influenced plus those who felt reassured) came to the counselor with their decisions about subsequent children already determined. This tends to support the concept that many families with genetic disorders intuitively make decisions about genetic risks and subsequent children long before they seek advice from a counselor. For such families the counselor simply provides a biologic explanation to support decisions already made. A similar conclusion was mentioned in a recent report by Hsia.[9]

If it is concluded that effective genetic counseling includes correct interpretation of counseling and use of the data in family planning, then we remain considerably short of our goal. However, our findings, which support those of Reynolds and co-workers[8] and Hsia,[9] suggest that family planning more often than not will be decided upon before counseling. On the other hand, a smaller but significant number of families will make decisions about future children based primarily on genetic counseling. For this group of parents, counseling becomes crucial. Thus it appears that improving understanding of counseling is a worthy goal.

Repeat clinic visits to review genetic advice given previously are helpful and are nearly unanimously requested by patients. However, our studies did not show a significant improvement in understanding of counseling relative to the number of clinic visits. As did Reynolds and co-workers,[8] we routinely send a typed summary of the genetic counseling session to each family. All families felt this was important, but again we have not been able to document that access to a written summary enhances the comprehension of genetic counseling.

It may be that long-term follow-up with continuous reinforcement of counseling may be crucial to effective comprehension of genetic risks. We have instituted such a program through public health nurses and the Department of Public Health. Evaluation of these results is in progress. Another appropriate alternative would be through private family physicians. It might be advantageous to a patient if his or her physician were thoroughly familiar with genetics, at least as related to the physician's area of clinical interest. It may well be an additional asset to the family for follow-up counseling to come from the health team member (nurse, physician and so forth) who will follow that family or patient for an extended time. This type of approach to genetic service is certainly possible. Skill in genetics and genetic counseling could be made part of postgraduate specialty training as, for example, they are parts of the requirements for a perinatal medicine subspecialty in obstetrics and gynecology.

It would seem reasonable that in the future, primary genetic counseling might be the responsibility of referring physicians, with medical geneticists filling a role as special consultants in counseling. Follow-up review or reinforcement of counseling could then be provided by a referring physician or, in some instances, by a consulting medical genetics team.

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Scleroma of the Nose and Pharynx

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Scleroma of the respiratory tract was first recognized just over a century ago. The disease is endemic in a number of North African, Central American and Latin American countries. However, it has been only rarely seen in the United States. The progression of scleroma takes place through three stages. The first stage of rhinitis has an early catarrhal phase which progresses to one of atrophic rhinitis. The second stage is seen as a proliferative granulomatous growth which obliterates the nasal fossae. The third cicatricial stage is usually accompanied by pronounced scarring and retraction of the tissues involved.

Because of the increased ease of international travel by both sea and air, more cases can be expected to occur in the United States. This paper is presented to alert physicians to suspect scleroma in any case of granulomatous disease of the respiratory tract.

SCLEROMA OF THE upper respiratory tract was first recognized over a century ago. It was described as a clinical entity by von Hebra in 1870, who called it nasal leprosy, hardnose and exuberant syphilis of the nose. Six years later, Mikulicz studied the microscopic histology. During the same year, Gerhard gave the first comprehensive description of laryngoscleroma. In 1882, von Frisch discovered the Klebsiella organism and suspected it to be the etiologic agent. However, it was not until 1900 that Gerber characterized the lesion as a chronic inflammatory process and described its histologic appearance.[1] Because the preponderance of cases presented with nasal involvement, it was often called rhinoscleroma.

At the Second International Congress of Otolaryngology held in Madrid in 1932, it was suggested that the term rhinoscleroma be changed to scleroma in order to emphasize that the disease may attack any part of the respiratory tract.[2] Similarly, it was suggested that such terms as syphilis of the nose, nasal leprosy, leprosy of the Slavics,[3] scleroma neonatorum[4] and scleroma respiratorium[5] be discarded in preference to scleroma alone.

Scleroma is particularly a disease of the young and middleaged adults. There is a slightly higher incidence in females. Most patients afflicted with the disease seem to belong to the lower economic class and have poor nutritional status. The disease

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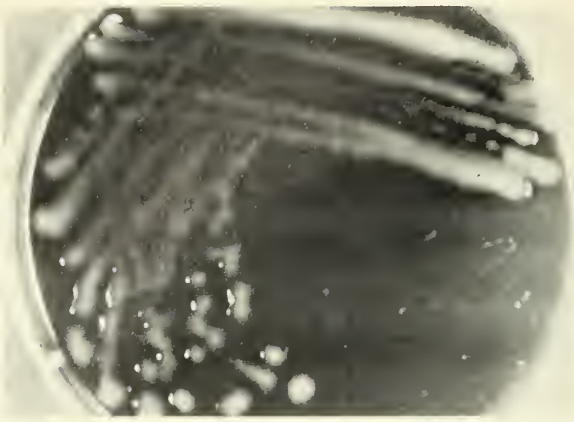

Figure 1.—A colony culture on blood agar medium showing typical Klebsiella rhinoscleromatis colonies.

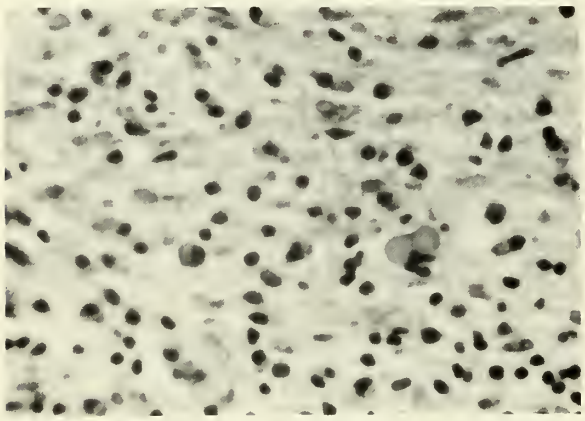

Figure 2.—Specimen taken during Stage II (granulomatous phase) of scleroma. Histologic section of nasal tissue shows abundant Mikulicz cells (foamy macrophage cells) and typical hyalinized Russell bodies in the central portion of the slide (reduced from 43×).

is not known to be contagious or familial as a rule, but Losageno reported 15 cases in one Italian family, and Hare and co-workers reported 7 cases in a single American family.[1] In the endemic areas of the province of Lublin in Poland, there is a higher proportion of familial incidence of scleroma observed among children as compared with adults.[6]

Scleroma is well-known in North Africa, Central America and Latin America—with the heaviest concentration of the disease being seen in the Guatemala-El Salvador region. Quevedo's Guatamelan series now consists of over 1,200 cases.[7] In neighboring Mexico, scleroma is frequently seen.[8] Scleroma is an extremely rare condition in the United States. The number of cases reported in native-born Americans is less than 60. With the increased ease of international travel by both air and sea in the last decade, one can expect the incidence of scleroma to increase in the United States.

Since scleroma may mimic various diseases of the respiratory tract throughout its stage of progression, this paper is presented to alert physicians to consider the possibility of scleroma in evaluating granulomatous disease of the respiratory tract.

Scleroma is a specific, chronic, progressive granulomatous disease of the respiratory tract. Because of the preponderance of cases with nasal involvement, earlier papers report the disease as rhinoscleroma. While most patients do, indeed, present with nasal involvement, the pharynx is involved in more than half the cases. In Mexico, laryngeal scleroma is evident in 15 percent of patients with respiratory scleroma. Tracheal and bronchial scleroma has been reported in 2 percent of such cases.[8]

Unusual cases of scleroma have been reported in the literature. The youngest age reported was in a newborn infant, with involvement of the middle ear. The oldest age reported was in a man of 68 years.[4] Scleroma has been reported with involvement of the paranasal sinuses.[9] Cervical lymph node involvement has been recorded.[10] Scleroma has also been shown to undergo intracranial extension.[11,12] Malignant changes have been reported in 5 percent of patients.[13]

Bacteriology

Klebsiella rhinoscleromatis is believed to be the causative agent of scleroma. K. rhinoscleromatis is a Gram-negative diplobacilli commonly known as the Frisch bacilli after its discoverer.[1] The slime layer of the K. rhinoscleromatis organism is considered to play an important role in the pathogenesis of the disease.

Klebsiella rhinoscleromatis grows poorly on the MacConkey's agar. Colonies are thick, grayish-white, slimy and mucoid and tend to string out when touched with a loop (Figure 1). On Gram staining, Gram-negative rods are seen. India ink smears show the presence of capsules. Some recent reports suggest that Klebsiella rhinoscleromatis may be identical with Type C of Klebsiella pneumoniae.[14]

Cellular Pathology

Histologically, one observes connective tissue containing Mikulicz cells, Russell bodies, plasma cells, lymphocytes, polymorphonuclear leukocytes, fibroblasts and the Gram-negative diplo-

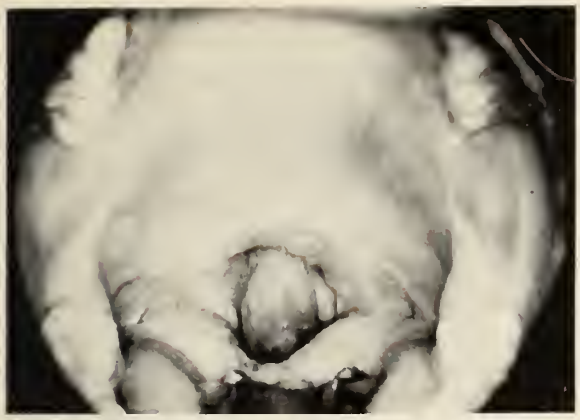

Figure 3.—View of the oral pharynx in Case 1 showing extensive hypertrophic lateral pharyngeal band scars with infiltration of the soft palate. The free margin of the soft palate is replaced by a dense band of scar tissue and the uvula is absent.

bacilli within the vacuolated portion of the Mikulicz cell.

The *Mikulicz cell* is considered to be a macrophage. It is seen as a large, foamy, mononuclear cell measuring up to 100 microns in diameter. It has a pale, reticular, ill-defined cytoplasm with an eccentric nucleus and central vacuoles.[15] If special bacterial stains, such as Giesma or Warthin and Starry stains, are used, one will find many Frisch bacilli within the vacuolated cytoplasm of the Mikulicz cell (Figure 2).

The *Russell bodies* are elliptical formations measuring 20 to 40 microns in diameter. They are smaller than Mikulicz cells but still twice as large as a normal plasma cell. They have a homogeneous brilliant red refractile cytoplasm (Figure 2). The Mikulicz cell is a major histologic feature of scleroma. However, the plasma cell, which undergoes some hyaline degeneration to become the larger Russell body, is not specific. Russell bodies may also be seen in any inflammation in which plasma cells are a prominent element. Such is the case in leprosy, malignant bubo and venereal granulomatosus.[8]

Cultures for K. rhinoscleromatis are most often positive during the granulomatous phase of the disease.

Nasal Scleroma

Nasal scleroma characteristically progresses through three stages. *Stage I* (rhinitis stage) begins with symptoms of *acute catarrh* that gradually progresses to symptoms compatible with *atrophic rhinitis*. At the onset of the disease, the patient may present with symptoms of acute rhinitis or a common cold. However, a feeling of malaise with hyperthermia and leukocytosis are conspicuously absent in scleroma. Later in Stage I, the early catarrhal symptoms become mucopurulent. There is a profuse, brownish discharge from the nose associated with pus formation within the nasal chambers. During this atrophic phase of Stage I, it is difficult to distinguish atrophic nasal mucosa of scleroma from that of ozaenae (atrophic rhinitis) or leprosy.

Stage II (granulomatous stage) is a proliferative stage in which nodular granulomatous outgrowths swell to fill the entire fossae of the nose. The nasal tip and the alae become enlarged and rigid. The lower nasal cartilages fan out and the soft tissue between them distends, producing an elephantiasis-like deformity.[16] At this stage, scleroma may clinically mimic carcinoma of the nose. Most patients present to their physician during this stage of the disease. It should be noted that during this stage of the disease, the characteristic Mikulicz cells and Russell bodies are most often present. The Frisch bacilli are usually abundant during this stage and readily cultured.

In *Stage III* (cicatricial stage), gradual development of fibrosis occurs with progressive scarring of the area. Visible contraction and deformities of the affected parts are seen as the inflammatory mass is replaced by extensive dense scar.

Reports of Cases

Case 1. In February 1973 a 23-year-old Mexican-born man was seen because of nose bleeds. The patient's history indicated that catarrh with nasal congestion had been present throughout most of his life. Because of nasal obstruction, a tonsillectomy was carried out in Mexico in 1970. Continued progressive nasal obstruction necessitated surgical operation on the nasal septum in Mexico in 1971.

In the present illness, there was a history of progressive nasal obstruction with foul smelling, brownish discharge. On examination, ballooning of the nasal alae was noted. The nasal septum was extremely widened bilaterally and inferiorly. There was total nasal obstruction due to extremely hard, keloid-like tissue filling the nasal cavity bilaterally. On examination of the oral cavity, thick granulation-type tissue along the free border of the soft palate and lateral pharyngeal bands was seen (Figure 3). Dense scarring of the soft palate had completely eliminated the

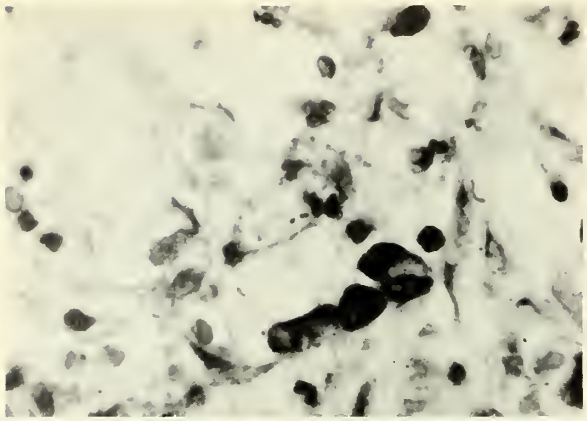

Figure 4.—Histologic section of biopsy tissue examined under oil emersion (reduced from 97×). Giemsa stain showed Gram-negative diplobacilli of Klebsiella rhinoscleromatis.

Figure 5.—Disc sensitivity testing on Mueller-Hintin medium. Tetracycline (upper right) was shown to provide most effective inhibition of growth of the organism.

uvula. Findings on indirect mirror examination of the larynx were normal. Results of otologic examination were within normal limits.

In April 1973 a biopsy was carried out and both nasal passages were packed with iodoform gauze to control bleeding. A pathology report confirmed the diagnosis of nasal scleroma. Two days later the nasal packing was removed. There was a dramatic and almost complete regression of the granulomatous tissue from the nose and nasopharynx. Because of the symptomatic relief following the biopsy, the patient failed to return for follow-up treatment.

In July 1974, because of persistence of disease and recurrence of symptoms, the patient returned for examination. Recurrent bilateral nasal masses were noted with thick crusting along the nasal mucosa, and a brown, foul-smelling discharge was seen in the nasopharynx. The nasal fossae were stenotic with ingrowth of thick, firm scar tissue. Polytomography of the nasal fossae showed intact bony margins of the nose and paranasal sinuses. The patient was taken to the operating room, where repeat biopsy confirmed the persistence of nasal scleroma. Disc sensitivities were carried out, and tetracycline proved to be the drug of choice. Administration of doxycycline hyclate (100 mg twice a day for six weeks) was begun.

Results of follow-up examinations in July 1975 showed excellent resolution of the scar tissue with a patent nasopharynx. The lateral pharyngeal band granulation tissue had regressed completely, and the foul-smelling discharge had disappeared.

Case 2. A 17-year-old Mexican-born girl was seen in March 1963 because of difficulty breathing through her nose. The patient gave a three year history of chronic nasal obstruction with catarrh. In 1962 nasal surgical procedures had been carried out in Mexico to relieve pronounced obstruction. On examination, protruding granulomatous tissue was noted which completely filled both nostrils and which bled when touched. Large granulomatous lateral pharyngeal bands were seen on examination of the throat. Findings on x-ray studies of paranasal sinus and chest were normal. Biopsy was carried out and the finding reported as "possible leprosy." The patient was brought to surgery for additional surgical excision of the proliferative mass. The pathology report identified the mass as scleroma, and Giemsa stains indicated the presence of Gram-negative diplobacilli (Figure 4). Administration of chlortetracycline hydrochloride was begun. Throughout the antibiotic therapy, nasal discharge and crusting continued to be present.

The patient was seen again in December 1963 with recurrence of large granulomatous tissue along the lateral pharyngeal bands and total nasal obstruction. The excessive tissue was treated with electrocautery and administration of chlortetracycline hydrochloride was begun again. The patient returned every six months because of recurrent disease and had to be taken to the operating room several times. In May 1967 the granu-

lation tissue had replaced both the right and left lateral pharyngeal bands. The uvula was no longer distinct but had been replaced by tense scar tissue along the free stenotic border of the soft palate. Repeat culture and disc sensitivities were carried out and chlortetracycline was shown to be the treatment of choice (Figure 5). However, the patient returned pregnant at this time and refused to accept further antibiotic therapy. She was not seen again.

Therapy

Quevedo reports that streptomycin administered for 21 days every three months over an average period of five years appears to give the most favorable response.[17] Streptomycin is effective given in large doses when scleroma is limited to the nose but not when the lower respiratory tract is involved. In such patients, the addition of tetracycline usually renders a good result. Treatment is started with 0.5 or 1 gram of streptomycin each day for two full weeks, depending on the tolerance of the patient to the drug. After one or two months, 1 gram of tetracycline is given every day. It is necessary to repeat this treatment periodically.[8] Administration of corticosteroids is helpful[6] in the granulomatous stage of the disease, during postoperative recovery and in patients with complete stenosis of the nose.[9] Findings on sensitivity tests of Frisch bacilli most often have shown tetracycline to be the treatment of choice. Disease limited to the nasal area may be effectively treated by partial rhinectomy in conjunction with tetracycline therapy. In all cases, identification of the organism should be achieved and antibiotic sensitivities obtained before beginning therapy.

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Medical
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Congenital Dislocation of the Hip

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Congenital dislocation or subluxation of the hip (congenital acetabular dysplasia) is a complete or partial displacement of the femoral head out of the acetabulum. The physical signs essential for diagnosis are age related. In newborns the tests for instability are the most sensitive. After the neonatal period, and until the age of walking, tightness of the adductor muscles is the most reliable sign. Early diagnosis is vital for successful treatment of this partially genetically determined condition. Various therapeutic measures, ranging from abduction splinting to open reduction and osteotomy, may be required. Following diagnosis in the first month of life, the average treatment time in one recent series was only 2.3 months from initiation of therapy to attainment of a normal hip. When the diagnosis was not made until 3 to 6 months of age, ten months of treatment was required to achieve the same outcome. When the diagnosis is not made, or the treatment is not begun until after the age of 6, a normal hip will probably not develop in any patient.

"There are persons, who, from birth or from disease, have dislocations outward of both the thighs; in them, then, the bones are affected in like manner, but the fleshy parts in their case lose their strength less; . . . They have the equal use of both their legs, for in walking they totter equally to this side and that."[1] Thus Hippocrates, in *About Articulations* described hip dislocations in the second century B.C.

CONGENITAL DISLOCATION of the hip is a genetically influenced condition in which there is a disturbance of the normal anatomy of the hip, either a complete dislocation of the head of the femur from the acetabulum or a partial displacement (subluxation) from the socket. Inadequate development of the roof of the socket (dysplasia) and laxity or elongation of the ligaments and capsule of the joint may be primary pathogenic features; both will be discussed in greater detail later. True congenital dislocation of the hip must be distinguished from teratologic dislocations such as may occur in arythrogryposis multiplex congenita, diastrophic dwarfism, Larsen's syndrome and other rare generalized mesenchymal disorders. It should also be distinguished from the paralytic dislocations which may occur in cerebral palsy, myelomeningocele, and following paralytic anterior poliomyelitis. In true congenital disloca-

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tion of the hip there are no other consistent abnormalities, with the possible exception of generalized joint laxity which is otherwise not disabling. It has been estimated[2] that 5,300 new cases occur annually in the United States.

Congenital dislocation of the hip has interested physicians and surgeons alike for centuries. Paletta, in 1775, was the first to use the term subluxation. As early as 1784 Camper is said to have commented on the preponderance of affected females. Dupuytren,[3] in 1826, described the autopsy findings in the case of a 74-year-old man who also suffered from "retention of urine, terminating fatally." He speculated that "the position of the lower extremities of the fetus in utero is such, that the thighs are very much bent on the belly, from which it follows that the heads of the thigh bones are continuously pressing against the lower and back part of the capsular ligament—a circumstance which, although without effect in well-formed individuals, might, I apprehend, have an injurious influence in such as are weak, or of lax, unresisting fibre. If this premise is conceded, there is not much difficulty in imagining that dislocation may result . . . "

Incidence

The incidence of congenital dislocation of the hip varies with the gene pool studied, high frequencies being reported in certain inbred Italian populations, in Israel, among certain American Indian tribes and among the Japanese. Substantial and very similar frequencies have also been reported from Sweden, Great Britain and the northern part of the United States,[4] an observation that suggests a similar genetic derivation of the inhabitants of these areas, as history in fact substantiates. The condition is by no means uncommon in other population groups, although in Africans and Chinese very low incidences have been reported. Incidence figures are somewhat confused by the fact that if careful examinations of newborn infants are routinely done, a very high proportion of unstable hips can be found.[5] The majority of these, however, become stable in the first few weeks of life,[5-7] and likely represent the substrate upon which other factors, probably environmental, act to produce true persistent dislocations, the frequency of which is about 1.1 per 1,000 live births in the United States.[4,8]

Etiology

Paré noted as early as 1678 that familial cases occurred, and all epidemiologic studies clearly indicate that heredity plays a very significant role in cause. The recurrence risk among siblings of affected persons is about 40 times as great as the incidence expected in the general population. Only one large survey of twins with congenital hip dislocations has been reported, in Germany, and a much higher concordance rate for monozygotic (41 percent) than for dizygotic twins (2.8 percent) was found. This clearly indicates the role of genetic influences, but also indicates that other factors must be operative. The proportions of affected second and third degree relatives is also increased, but drops rapidly toward the incidence found in the general population with decreasing closeness of the relationship, thus conforming most closely to the model for polygenic inheritance.

Among the environmental factors closely related is breech delivery, which is reported as having occurred in 11 to 40 percent of cases,[9] in contrast to the expected 2 to 4 percent. In addition, some series report a birth order effect, with first-born children being most commonly affected.[10] Several surveys have also reported an increased incidence of congenital dislocation of the hip during the winter months.[11,12]

Additional environmental factors which have attracted attention are the supposedly deleterious effects of swaddling, a custom in certain European and American Indian populations,[13] and the allegedly salutary effects of carrying an infant astride the back. The former holds the hips adducted, whereas the latter holds the hips abducted, consequently allowing better seating of the femoral heads in the sockets. In implied agreement, the American Academy of Pediatrics has adopted as a symbol a modified version of the famous Della Robbia terra-cottas (of the Spedale degli Innocenti in Florence) of a swaddled infant in which the constricting garments have been loosened. Results of experiments with animals have in fact shown that dislocations of the hips can be provoked by immobilizing the hindlegs in abnormal positions; however, the general caveat regarding extrapolation from animals to humans should be heeded.

Some authors[13] believe that sudden extension of the hip after delivery of an infant, as might occur in the common practice of holding the newborn infant by the ankles and slapping the back

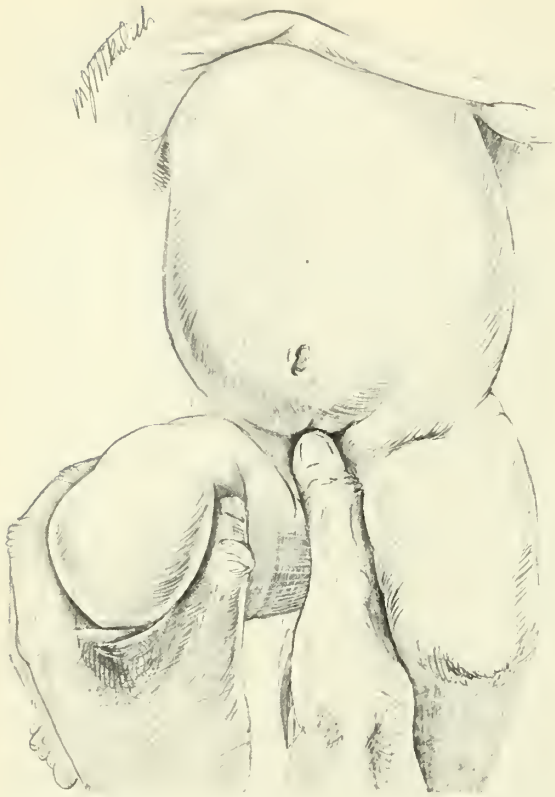

Figure 1.—Barlow's maneuver. With one hand grasping the symphysis in front and the sacrum in back, lateral pressure is applied to the medial thigh with the thumb of the other hand while longitudinal pressure is applied with the palm to the knee on the side being examined. The hip, which has been flexed 90 degrees, is then adducted. A positive sign is a sensation of abnormal movement, indicating dislocation of the femoral head from the acetabulum. The hands are reversed for examining the other hip. This sign and Ortolani's sign may be found only in the first few weeks of life. (Reproduced by permission from Specht EE: Am Fam Physician 9:88-96, Feb 74)

Figure 2.—Ortolani's maneuver (sign of jerking into place). After provocation of a dislocation by Barlow's maneuver, as shown in Figure 1, the hip should be abducted to about 80 degrees while the proximal femur is lifted anteriorly with the fingers placed along the lateral thigh. A positive sign is a sensation of a jerk or snap with reduction into the socket. A click is not necessarily heard and a click wihout a sensation of abnormal motion is probably not significant. (Reproduced by permission from Specht EE: Am Fam Physician 9: 88-96, Feb 74)

to drain respiratory secretions, is deleterious, at least in the presence of laxity of the capsule and ligamentum teres.

It has long been recognized that females are about five times more commonly affected than males, and a hormonal effect has been inferred. Some observers[14] have in fact reported that estrogen excretion levels are higher in affected infants than in normals, but others[15] have failed to confirm this. The belief, however, that female infants are more sensitive to the hormones of pregnancy and that these hormones cause greater ligamentous laxity than in the male, holds some currency. Findings in several studies[16] have shown that both patients and first degree relatives of patients have an unusual degree of joint laxity. This is probably inherited as an autosomal dominant trait, therefore giving an incidence of joint laxity in 50 percent in the offspring of an affected person. Obviously this far exceeds the risk factor in congenital dislocation, but environmental factors vary, and necessarily modify the genetic predisposition in such families.

Results in other familial studies[16,17] indicate that defective development of the acetabulum, with a resulting shallow socket (primary acetabular dysplasia), a concept popularized by Hart,[18] may be polygenically inherited, and that those cases diagnosed after the neonatal period may represent the dysplastic rather than the ligamentous laxity type.[19,20] It is thus possible that two genetic systems, one autosomal dominant and the other polygenic, may interact and in turn be acted upon by environmental factors.

Figure 3.—Adduction contracture. In the infant or child over 1 or 2 months of age, limitation of abduction of the flexed hips is probably the most reliable sign of congenital dislocation. Note the prominent "bowstringing" of the adductor tendon in the proximal thigh on the dislocated right side, as well as the limitation of abduction in comparison with the normal side. (Reproduced by permission from Specht EE: Am Fam Physician 9: 88-96, Feb 74)

Genetic Counseling

The empiric recurrence risks have been calculated[21] as follows: (1) with normal parents, the risk to subsequent brothers of an index patient is 1 percent, to subsequent sisters, 11 percent. (2) If one parent has a congenital hip dislocation the risk to a son is 6 percent, to a daughter 17 percent. (3) If there are one parent and one child in an affected family, the risk to a second child rises dramatically to 36 percent. The implications of these data are obvious; at the very least careful and repeated examinations of all infants in such families must be started at birth.

Problems in Early Diagnosis

There is general agreement among authorities that the earlier treatment is started, the better the prognosis—a concept popularized by Putti.[22] Considerable advances have been made since the adoption of Ortolani's technique[23] for diagnosis in the newborn period. Von Rosen[24] in 1962 reported his results in the application of Ortolani's technique, which is described in the accompanying illustrations. This and Barlow's[6] description of a maneuver which provokes dislocation in unstable hips have undoubtedly greatly increased the numbers of infants who present for early treatment. Every physician who examines children should be thoroughly conversant with these techniques which are described and illustrated again (Figures 1 and 2) without apology. One bit of confusion regarding Ortolani's "sign of the click" bears some mention. The English word click is an unfortunate translation of the Italian *scatto* which has no English cognate, and which means a "jumping up" or "jerking into place," which in fact is what happens when the dislocated or subluxed hip is abducted while being held in 90 degrees of flexion. There is nothing audible about this "click," and in fact most clicks are not significant.[15,25] It is the palpable, and sometimes visible, reduction of the dislocated head into the socket that constitutes a positive finding.

Barlow's maneuver consists essentially of provoking a dislocation by longitudinal pressure along the femur, with the hip flexed and adducted and then reducing it in the same manner as in the Ortolani maneuver. The infant must be relaxed while these maneuvers are being carried out, and a crying infant must be reexamined; in fact, repeated examinations[26,27] throughout the first year of life are essential if cases are not to be missed.[25,26,28-30] Unfortunately, roentgenography cannot be relied upon to resolve doubt remaining after clinical examination[25,26,31] in the newborn period. Only following ossification of the capital femoral epiphyses at age four months or so can roentgenograms clearly delineate the relationship of the femoral head to the acetabulum.

Ortolani's and Barlow's tests are of great value in the first few weeks of life, while the hip can still be reduced easily; however, once the head of the femur has migrated laterally and proximally onto the lateral surface of the ilium and the adductors have become relatively shortened and tight, other signs must be sought. Following the first month or so of life in an affected infant, abduction of the flexed hip, normally possible to at least 60 or 70 degrees,[4] becomes limited (Figure 3). It is of course helpful to compare abduction on one side with the other, but it should be borne in mind that bilateral involvement is not uncommon, in fact more common in some series,[31] and one must know the normal measurements. Shortening of the extremity (Figure 4), consequent to proximal displacement of the femoral head, can be detected by careful comparison of the lengths of the extended legs or by the method of Galeazzi in which the hips and knees are flexed to about 45 degrees while holding the heels equidistant from the buttocks on the examining table. In the bent-knee method the dislocated side will show the knee to be lower, that is closer to the table.

Asymmetry of the inguinal and buttocks skin creases, and relative prominence of the greater trochanter on the affected side are all useful later signs. Asymmetry of the thigh folds, however, is not useful—yielding a very high incidence of false positives. After the child begins to walk, very

late in the game to make a diagnosis, the characteristic painless abductor lurch (Trendelenberg gait) toward the affected side, and an external rotation attitude of the involved leg may be noted.

We still find late cases and the question has been raised[20] if they represent a different group of "stiff hips" than those which present early with instability. This would fit nicely with the thesis of two genetic entities[16] with a common end result, but as yet the proof is lacking.[20] In any case, it should be reiterated that one normal examination in the nursery does not relieve the physician of further diagnostic efforts.

A significantly higher incidence of congenital dislocation and subluxation of the hip in infants affected by congenital muscular torticollis has been noted by two groups of authors.[32] The frequency of dislocation and subluxation combined was 20 percent in one series of infants who had presented for torticollis. The diagnostic inference is clear; all such infants should be carefully examined, and probably x-ray studies should be done as well.

Figure 4.—Asymmetry of the thigh and inguinal creases. Bilateral asymmetry of the thigh creases alone is an unreliable sign but asymmetry of the inguinal or gluteal creases, especially with apparent shortness of the thigh, is a good indication of hip dislocation. Note that the infant's left knee is higher than the right and the prominence of the greater trochanter on the left is more pronounced and more proximal than on the right. The left hip is dislocated. (Reproduced by permission from Specht EE: Am Fam Physician 9:88-96, Feb 74)

Roentgenographic Features

The diagnosis of congenital dislocation is essentially a clinical one; however, roentgenograms can be of considerable help—especially in following progress under treatment. Efforts have been made[6,28,33] to use roentgenograms in the newborn period, but opinions vary considerably as to their efficacy,[11,25] and most authorities agree that normal findings on x-ray films do not exclude the possibility that a dislocatable hip was x-rayed while in the reduced position[31] and the finding therefore gave a false sense of security (Figure 5). After the age of 4 to 6 months, at which time the capital femoral epiphyses ossify, roentgenograms in the anteroposterior and "frog-leg" lateral positions will satisfactorily delineate the relationships between the femoral head and the acetabulum. A horizontal line drawn transversely across the pelvis through the centers of both triradiate

Figure 5.—This roentgenogram shows the difficulty in evaluating x-ray studies of the hips in newborns. Although the hips appear symmetric and are not obviously displaced superiorly, there is a suggestion of lateral subluxation bilaterally. The acetabulums appear normal. This infant had positive Barlow and Ortolani signs and was treated with a splint because of the positive clinical findings, in spite of the equivocal x-ray findings. (Reproduced by permission from Specht EE: Am Fam Physician 9:88-96, Feb 74)

cartilages in the acetabula and a vertical line dropped from the lateral margin of the bony roof of the socket to intersect the horizontal line at right angles is useful in detecting abnormally lateral and superior position of the capital femoral epiphyses. In a normal hip, the ossific nucleus of the femoral head lies below the horizontal line and medial to the vertical line. As subluxation occurs the ossific nucleus is either bisected by the vertical line or lies lateral to it. Similarly, proximal migration of the femoral head, which ultimately comes to rest superior to the horizontal line, occurs.

Another useful measurement in following progress in treatment, and in diagnosis in late cases at least, is the so-called acetabular index[34] (Figures 6 and 7) which might better be called the roof-slope angle. Lines drawn along the acetabu-

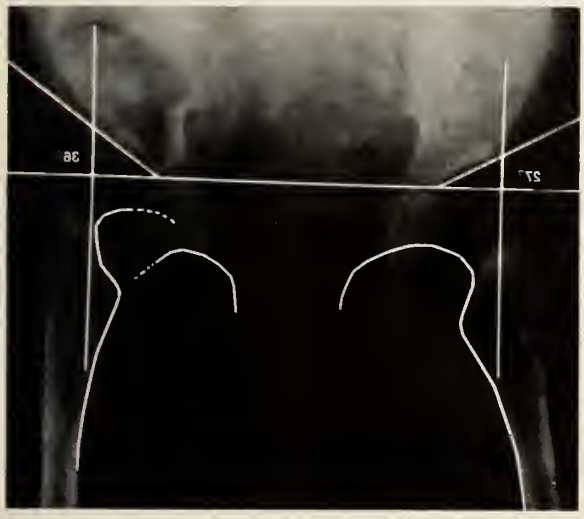

Figure 6.—Shenton's lines and the acetabular index. In this patient, the left hip is obviously displaced both laterally and superiorly, as shown by the disruption of Shenton's line (medial neck to superior obturator fossa) on the left. On the normal right side, the typical shepherd's-crook configuration of this imaginary line is preserved. The acetabular index, which simply indicates the slope of the roof expressed as degrees of angulation from the horizontal, is increased on the left side. (Reproduced by permission from Specht EE: Am Fam Physician 9:88-96, Feb 74)

Figure 7.—A frog-leg lateral view of the same hips as shown in Figure 6. This view shows the relative underdevelopment of the capital femoral epiphysis on the patient's left side. Delayed development cannot be detected until this ossification center becomes visible on x-ray studies, usually at 4 to 6 months of age. (Reproduced by permission from Specht EE: Am Fam Physician 9:88-96, Feb 74)

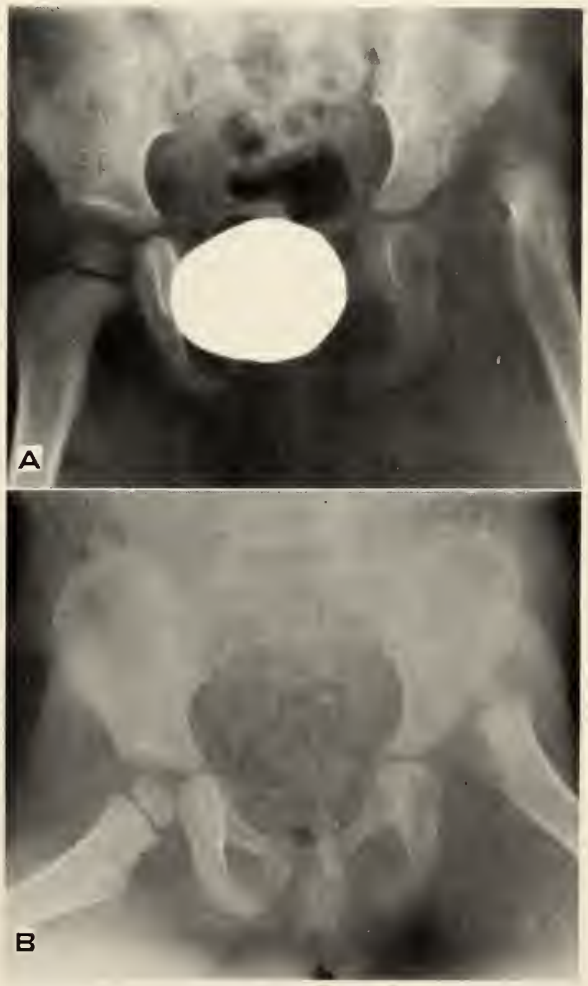

Figure 8.—Typical superior displacement of the left hip, as seen in the anteroposterior view **(A, above)** and the frog-leg lateral view **(B, below)**. Note the failure of acetabular development and the relative hypoplasia of the entire femoral head and neck on the left. Note also that the left hip cannot be abducted as well as the right hip, because of tightness of the adductor muscles. This is a roentgenogram of a 3-year-old girl, untreated at the time. (Reproduced by permission from Specht EE: Am Fam Physician 9:88-96, Feb 74)

lar roof and extended to intersect the horizontal line will form an acute angle which is easily measured, and which is increased in dysplasia and dislocation. This angle normally becomes more acute with increasing age. The normal values for this angle have been described[27] and can be helpful in diagnosing dysplasia, particularly if there is a pronounced discrepancy between the two sides. With sufficiently early and successful treatment the acetabular index declines to normal, whereas the slope increases and assumes a bilabiate appearance if dislocation persists (Figures 8A and 8B).

A line can be projected along the medial portion of the femoral neck, the calcar femorale, and extended medially to intersect the margins of the obturator foramen in the anteroposterior projection (Figure 6). Normally this medial projection will correspond exactly with the superior margin of the foramen; if there has been proximal displacement of the head, however, the line will be disrupted and will pass more toward the triradiate cartilage. An additional measurement of value in appraising adequacy of reduction and coverage of the head by the roof is the center-edge angle of Wiberg[35] in which an angle is constructed by a line drawn from the center of the head through the lateral margin of the acetabulum, intersecting at that point with the vertical line described above. This "CE angle" is normally more than 20 degrees, and declines to zero as the center of the laterally-displaced head comes to lie on the vertical line.

Arthrography[36] is used by some surgeons to evaluate adequacy of reduction and to delineate the condition and position of the acetabular labrum (the limbus) and other soft tissues interposed between the head and the medial wall of the acetabulum, but its usefulness is limited. In our hands tomography[37] has been useful to ascertain that a concentric reduction, without posterior displacement, has been obtained when the patient is in a cast or splint.

Treatment

Treatment of congenital dislocation of the hip is perhaps more clearly age-related than any other condition in medicine, a fact that reflects progression of secondary pathologic changes. In an infant with dislocatable hips due to ligamentous laxity (a primary change occurring before the development of secondary changes, such as increased slope of the acetabular roof, adductor tightness and actual dislocation of the head) simple abduction splinting by any of several devices[6,11,24,31,38] will almost invariably result in a normal hip.[6,11,24,28] In fact such treatment is probably best considered prophylactic.

Following the first few weeks of life, however, the difficulty in attaining normal clinical and roentgenographic findings is greatly increased[38-40] hence the considerable efforts expanded on early diagnosis and treatment.

Although there are exceptions,[41] most orthopaedic surgeons[42,43] believe that nonoperative management, as propounded by Putti[22] some 40 years ago, is best until the child begins to walk, and perhaps later. Opinions vary on details and a review of the literature suggests that there are no hard data on precisely when conservative management ceases to be appropriate. Most would agree that up to the age of 6 months or so, abduction splinting, or the Pavlik harness[44] currently gaining favor, is indicated until the clinical and roentgenographic findings revert to normal in both dysplasia without frank dislocation and in dislocation. This may be a matter of some months, and a period of immobilization equal to the elapsed time between birth and initiation of treatment has been suggested as a guideline to duration. Demonstration, by x-ray films taken in the abduction device, that the hip is in fact reduced is essential. Between the ages of 6 and 12 months, gentle manipulation under anesthesia may be required to attain reduction. This should be followed by a period of immobilization in a cast in the position of maximal stability. In recent years there has been increasing awareness of the danger of prolonged immobilization in either the frog-leg (Lorenz) position of extreme abduction[45] or the internal rotation position of Lange—both of which subject the posterior retinacular vessels, which supply the capital femoral epiphysis, to extreme mechanical distortion. It is commonly believed, and probably correctly so, that these bizarre positions may contribute to the development of avascular necrosis of the femoral head (osteochondrosis), and instances have been reported in which the previously normal hip in unilateral cases developed avascular necrosis during treatment.[46] It should also be noted that this complication is never seen in untreated patients, and can fairly be said to be iatrogenic. In an effort to avoid this catastrophe, a position involving somewhat more flexion but considerably less ab-

Figure 9.—Complications of treatment. The left hip is displaced superiorly and laterally from the acetabulum, Shenton's line is disrupted and the capital femoral epiphysis has undergone avascular necrosis. This hip had been treated by closed reduction and immobilization in a plaster cast. Prognosis is poor. (Reproduced by permission from Specht EE: Am Fam Physician 9: 88-96, Feb 74)

duction of the hips, a so-called "human position," has been advocated.[45] Conclusive data on the incidence of complications in its use are not yet available.

Casts used during this age range will become uriniferous quite quickly, and skin problems may arise. In some instances the substitution of a plastic splint or the cloth harness of Pavlik may be satisfactory after a month or two of plaster immobilization, but again, maintenance of a concentric reduction must be confirmed by biplane or tomographic roentgenography.

Between the ages of 1 and 3 years, secondary changes such as increased slope of the roof of the acetabulum, inversion of the limbus, fibrofatty masses filling the acetabulum, increased femoral anteversion (which will be discussed later), poorly formed femoral head, thickening and hourglass constriction of the capsule, hypertrophy and elongation of the ligamentum teres, and tightness of the muscle origins and insertions about the hip (particularly the adductors and the iliopsoas) are fully developed. Management during this period is the subject of considerable discussion and diversity of opinion. Closed reduction following preliminary skin traction[39,42,43,45] is probably the method used most between ages 1 and 2. Preliminary subcutaneous adductor tenotomy[39,43] has an increasing number of advocates in keeping with the desire to minimize the risk to the vascular supply of the head (Figure 9). When the adductors have shortened and the head is lying high on the lateral wall of the ilium, any attempt to reduce it into the acetabulum, several centimeters distally, and at the same time to abduct the thigh to achieve stability of the reduction will necessarily exert leverage on the head and cause compression of the vessels, which it is believed can be lessened by sectioning the structures medial to the head and neck. Some authorities hold that the adductors are of major concern in this regard, while others[41] believe the focus of attention should be on the iliopsoas tendon. Statistical validation of either position is lacking, but animal studies have indicated a decreased incidence of vascular changes following adductor tenotomy.

Open reduction enjoys some advocacy[41] before 2 years of age, and is increasingly used in those over 2 years old;[39] it is currently usually combined with osteotomy of the innominate bone,[47-53] and sometimes with derotational osteotomy of the proximal femoral diaphysis to correct anteversion. Two kinds of innominate osteotomy have been described for use early in life and have approximately the same usefulness. The pericapsular osteotomy of Pemberton[47,50,52] depends on some plasticity of the triradiate cartilage to allow a hinge motion to occur and hence may be more useful in younger children and where it is desirable to make the socket somewhat smaller. The procedure described by Salter[48,49,51,52] lends itself better to management of older children because the bend comes by levering the wing of the ilium laterally and downward over the femoral head after it is reduced into the acetabulum. We have seen instances where the osteotomy was neatly done but the head was never reduced into the true acetabulum. Both of these procedures should be done *only* if the head can be pulled down opposite the true socket by preliminary traction, and the acetabulum *must* be identified at operation by its normal cartilaginous surface, which is invariably present.[54] To conceive of these procedures as primarily innominate osteotomies is erroneous. They are primarily open reductions with osteotomies to improve bony coverage of the head.

Another promising advance in managing this difficult problem is the addition of subtrochanteric resection osteotomy[55-58] in which 1 to 2 cm of bone are excised from the proximal femur, de-

pending on the tension of the muscles about the hip as seen at the operating table. One of the remaining problems in open reduction and innominate osteotomy is the pernicious tendency of the head to redislocate while in the cast, or perhaps even while the cast is being applied. This is a consequence of two factors, persistent femoral anteversion and tension on the muscles crossing the hip joint. Both of these factors can be dealt with at one sitting by subtrochanteric resection and derotation osteotomy combined with open reduction. The concept of derotation osteotomy in the management of femoral anteversion is not new,[39,59-61] and while some contend it is unnecessary, others are equally convinced it is on occasion critical to obtaining the best result. The question of future leg-length discrepancy must inevitably arise when bone is resected from one leg, and no long-term results are yet available; however, it should be noted that sacrifice of 2 cm or so of bone, the average necessary, will likely eventuate in only a ½ cm discrepancy because of the well-known tendency of the adjacent epiphyses to overgrow following fracture and other insults. A ½ cm, or even a 1 cm disparity in leg lengths is negligible compared to the long-term sequellae of persistent hip dislocation or repeated operative intrusion and resultant loss of motion.

In children over the age of 7 or 8 who first appear for treatment, and perhaps in some in which there has been failure of previous treatment, the advisability of salvage procedures arises. In times gone by the Hey-Groves-Colonna capsular arthroplasty[62-64] and various shelf procedures[65,66] were widely used and still enjoy some support,[67] but other authors[68,69] contend that at least in the bilateral cases nothing should be done after the age of 7 or so. Another procedure gaining advocacy in older children and young adults with persistent dislocations is the innominate osteotomy of Chiari,[70] which should be viewed as a salvage procedure when traction and reduction do not appear feasible. In this procedure the ilium is cut through above the femoral head, which is then displaced medially under the buttress of the osteotomy. Preliminary results are encouraging, and the provision of bony stock above the femoral head will undoubtedly be helpful should subsequent reconstruction be necessary.

Other procedures which should be mentioned for completeness, but which appear to have fallen from favor are the so-called pelvic support osteotomies,[71] in which the proximal femur is transected, the proximal fragment is adducted against the pelvis and the distal fragment is abducted relative to the proximal. It is held that the displaced proximal fragment helps to support the pelvis, minimizing the abductor lurch which occurs during gait. Early postoperative results have been described as encouraging, but there are no series of significant size over a period of years, and some question must arise as to the effect on the knee of such realignments of the proximal femur.

Complications and Prognosis

The most common complications of treatment are failure to obtain concentric reduction, loss of motion from operative intervention, the possibility of postoperative infection of the joint and avascular necrosis of either the affected or the normal hip (Figure 9). Premature epiphyseal fusion of the knee has also been described,[72] Sequellae of failure to obtain reduction, or of no treatment, are the development of premature degenerative joint disease.[36,73] We have seen symptoms of easy fatigability and discomfort occur in adolescence; however, most patients do remarkably well at this age in spite of an unsightly lurching gait, in which the center of gravity is shifted toward the affected hip during the stance phase of gait, thus causing the trunk to sway laterally. This occurs because the lever arm of the abductor muscles of the hip, which must maintain the pelvis level, is mechanically deficient. This allows the pelvis to tilt abnormally away from the affected hip when it is bearing weight. The effort to compensate for this deficiency and prevent falling results in the shift of the center of gravity described above.

The usual course of a dislocated hip is one of increasing pain and disability during early middle age, a time when most women need to remain active in the care of their families. During this period many will require reconstructive arthroplasties[74,75]— a subject in itself and beyond the scope of this paper. Thus one can see the crucial need for early diagnosis and skillful management. With the virtual disappearance of poliomyelitis as a crippler of young people, there is probably no single area in which the primary care physician can be so effective in the prevention of late crippling. Nowhere else is the proverbial ounce of prevention (in this context a high index of

suspicion and a willingness to examine carefully hundreds of babies in order to identify the one at risk) of greater curative value to the patient. To reiterate the words of Putti "La cura preambulatoria non é piú una vuota aspirazione."

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The Obese Patient

To have a significant impact on life expectancy, in the actuarial sense, one has to have a weight which deviates by more than 30 percent from the expected weight for that person at his particular height. Basically, if you are overweight, you have a risk that is about 4.9 times as great of being diabetic, about 3 times as great of being hypertensive and of developing hypertensive cardiovascular disease, and about 2½ times as likely to develop gallbladder disease with gallstones and complications therefrom. So, for people who are significantly overweight, there are substantial medical risks associated with that weight which, therefore, allow the physician, because of the risk of the obesity as a factor in the development of these conditions, to employ methods which have a somewhat higher risk-to-benefit ratio than for a patient who is less than 30 percent overweight and who has no medical problems that can be detected.

—GEORGE A. BRAY, MD, *Torrance, CA*
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Specialty Conference

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Pulmonary Alveolar Proteinosis

Respiratory Medicine Rounds of Stanford University Hospital

JAMES R. PHILLIPS:* *The patient for discussion today is a 35-year-old man of French and Eskimo descent. He was in excellent health until June 1967 when he reputedly had pneumonia. It is not known whether an x-ray film was obtained. Treatment was with antibiotics. Fever and sputum production decreased and he returned to his baseline of good health. He noted dyspnea on exertion for the first time five months later (November 1967) while playing sandlot basketball. His physician obtained a chest x-ray study which showed bilateral infiltrates. Although afebrile, the patient was treated with several antibiotics without change in symptoms or improvement in findings on an x-ray film of the chest.*

We do not have the original x-ray film, but the first one that was taken at Stanford shows bilateral infiltrates, more pronounced on the right (Figure 1). Dr. Simon, what do you think about this chest x-ray film?

LAWRENCE SIMON:† Many interstitial diseases are described by radiologists as reticulo-nodular infiltrates. Some findings are supposed to be classic for alveolar filling processes, like the presence of air-bronchograms. These are seen on this chest x-ray film. It is important to note how far out they are seen. In this particular film, there are air-bronchograms seen at the right base. Classic honeycombing or relatively large cystic areas scattered throughout the lung correlate pretty well with the pathology of interstitial disease and are not seen here. This suggests that in this patient an alveolar and not an interstitial process is present.

EUGENE ROBIN, MD:‡ The formal x-ray criteria for distinguishing between interstitial disease and alveolar disease should be noted. In pure interstitial disease, there is a blurring of the hilar margins since the interstitial space extends over the origin of the bronchi and vessels. This gives the appearance of blurring, as though the patient had moved while the x-ray film was taken. The second criterion is that the densities in interstitial disease tend to run every which way because there is no particular spatial orientation of the pulmonary interstitium. At least early in the process, this gives you linear densities. The third criterion is that very early in the course of interstitial disease, the alveolar septae become prominent. They stand out in the same way that the airways stand out in intraalveolar disease, and give rise to Kerley B lines. Finally, interstitial disease is associated with the appearance of honeycombing.

The formal criteria for pure intraalveolar in-

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ABBREVIATIONS USED IN TEXT

CVP = central venous pressure
DIP = Desquamative interstitial pneumonia
DLCO = diffusing capacity of the lung for carbon monoxide
LDH = lactic dehydrogenase
PAP = pulmonary alveolar proteinosis
Po_2 = oxygen partial pressure
SSKI = saturated solution of potassium iodide
PAS = periodic acid Schiff

volvement are, first of all, the presence of air-bronchograms which are believed to arise by the penetration of a group of alveoli by small airways. Second, it is clear that the basic radiologic unit of the lung is not a single alveolus but a collection of alveoli giving rise to an acinus. The so-called alveolar pattern is more accurately described as an acinar pattern, rather than an alveolar pattern. Therefore, individual densities, before they become confluent, tend to be round, since the geometry of a group of alveoli clustered in an acinus is a more or less round or elliptoid structure. Third, confluence of these round densities tends to show a ground glass appearance. As you look at the lung, it shows not only a smooth opacity, but it is "soft-smooth." It is difficult to convey the sense of softness versus hardness seen on a chest x-ray film, but fibrotic markings are frequently very white and very dense, while these are less dense and give you a homogeneous appearance. Many pulmonary diseases involve both the intraalveolar and interstitial spaces and the features seen on an x-ray film are mixed—but these criteria are often useful in the differential diagnosis of diffuse infiltrative lung disease.

Dr. Phillips: Sputum and skin testing studies were carried out and findings were negative. The patient's father had died of "fluid on the lungs" but the patient believed this was of cardiac origin. His occupational history was limited. He had only worked for a brief period in a smelter where there were open vats of molten lead and tin. Following this, he had worked briefly as a forklift operator in a canning factory. In the absence of evident cause for the patient's condition, an open lung biopsy was carried out. Findings showed the classic features of alveolar proteinosis. The patient was transferred to Stanford for treatment and follow-up.

Serum lead levels were obtained at the first admission and were reported as 100 micrograms (μg) per 100 ml (substantially elevated). On the

Figure 1.—Pulmonary alveolar proteinosis in a young man.

first lavage, there were measurements of lead content on the material obtained at lavage. It varied in lead content between 15 and 20 μg per 100 ml. The significance of this finding is not known. Following this, serum lead levels have been within normal range. Lactic dehydrogenase (LDH) levels have been modestly elevated. Therapy consisted only of pulmonary lavage at periods of severe functional abnormalities until January 1969 when Dr. Robin saw the patient as a visiting consultant and suggested administration of saturated solution of potassium iodide (SSKI). The patient took this intermittently until 1972 when it was discontinued.

Following a lavage in January 1969, chills and fever and anterior chest pain occurred. A density was noted in the right lung on a chest x-ray study. Follow-up films, made the next day, showed increase in this density. Administration of heparin and penicillin was begun. Three days later severe epistaxis occurred during which the hematocrit fell from 50 to 36 percent. Administration of heparin was stopped but penicillin was still given and the patient responded well. No pathogen was recovered. The patient had two more bouts of pneumonia in 1969, responding to penicillin each time. He has had none since then. There is complaint of periodic increase in sputum production and low-grade fevers, which the patient treats at home with antibiotics for three or four days.

We have the results of a large number of pulmonary function tests dating back to the patient's first Stanford visit in 1968 (Table 1). In all, four lavages have been done since 1969: between

February 16 and 23, 1968; August 5 and September 23, 1968; January 8 and March 6, 1969, and January 8 and March 5, 1970. Symptomatically, the only time the patient noted real improvement was following the first lavage. Pulmonary function test findings and symptoms were used as criteria for the subsequent lavages. The third lavage was done when oxygen partial pressure (Po_2) reached the 50's for the first time and the fourth lavage was done when Po_2 decreased to 48.

I will describe how the first lavage was done. A total of 15.8 liters of heparinized saline was used and 15.9 liters of material was returned. This contained a grungeous, gray-white material with the consistency of farina. Particles were obtained throughout the lavage but the effluent was much less dense toward the end of the procedure.

DR. SIMON: *When a lavage is done, what is the usual percentage of return?*

DR. ROBIN: On the average, in the absence of obstructive lung disease, about 90 percent; in patients with obstructive lung, considerably less than 90 percent because of liquid trapping in the lung.

DR. PHILLIPS: Subjective symptoms in lung disease are something we discuss frequently. I saw this patient first in July 1974 when he made a nonscheduled visit to the chest clinic complaining of dyspnea, shortness of breath, exercise intolerance and difficulty in working as a forklift operator. He felt his condition had deteriorated greatly. Findings on physical examination were normal except for some bronchovesicular breath sounds in both lung fields. Pulmonary function testing was done on that visit. The patient had become fairly sophisticated at interpreting pulmonary function tests during the course of the illness. At the time of testing, he looked at the values, found them essentially unchanged and immediately lost all of his symptoms. Since then he has had absolutely no symptoms. Current x-ray studies are stable showing extensive intraalveolar disease. The patient has continued to smoke and has gained 10 pounds.

During a stay in hospital, a sputum smear suggested the presence of organisms that looked like Nocardia. This was not confirmed. Nocardia has often been implicated as a secondary invader in patients with this disease and sometimes theorized as a possible etiologic agent.[1] A similar picture can be produced in animal models by Cryptococcus.[2]

DR. ROBIN: There is a fair incidence of fungal infection in this disease, particularly in patients who have received steroid treatment. In the first patients with proteinosis and fungal infection, Nocardia was seen so that this association has become fixed in the literature. The association is probably with fungal infection in general and not specifically with Nocardia. Fungal infection may develop in the absence of steroid treatment. However, steroid therapy does not improve the disease and does increase the possibility of fungal infection. Therefore, patients with pulmonary alveolar proteinosis should not be treated with steroids. In patients who show deterioration, the possibilities of complicating fungal infection should be carefully investigated.

RAYMOND LASURE, MD:* I have read one of the original accounts of the delineation of this disorder by Rosen, Castleman and Liebow.[3] They thought that it might be related to pneumocystis pneumonia and that this perhaps represented a differential state in the evolution of the disease.

There is another interesting line of thought as to cause. Desquamative interstitial pneumonia (DIP) is a disease in which pathologically one sees numerous granular pneumocytes packing the alveoli. Some people think that material is surfactant-like if not surfactant. Some have suggested that perhaps DIP is a stage in which the pneumocytes are still viable, while pulmonary alveolar proteinosis (PAP) may be deterioration of the pneumocytes.

JAMES THEODORE, MD:† A historical perspective on lavage: When the disease was first described, it was felt to be a fatal disease with rapid progression. Ramirez in Maryland suggested that lavage would lead to remission.[4] It turned out that the composition of the lavage fluid was unimportant. We now feel that lavage is usually not indicated because of accumulating evidence of spontaneous remission.

PATRICIA LYNNE-DAVIES, MD:‡ *Looking at the function data before and after lavage, there appears to be an improvement in the diffusion capacity but we do not see much change in the other measurements. What would you expect to see just a few days after lavage?*

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TABLE 1.—*Pulmonary Function Data*

Predicted Date	*VC 4800*	*TLC 6400*	*DLCO 34.2*	*P_{O_2} 90*
2-16-68 *	2874	3600	8.4	66
2-23-68	3048	3665	11.9	62
3-25-68	3870	4920	13.4	85
8- 5-68 *	3650	3966	17.0	61
9-23-68	3370	3868	18.0	70
11-26-68	3135	3825	11.7	64
1- 8-69 *	3128	3477	11.9	52
3- 6-69	3226	3566	10.3	58
6-13-69	3284	3617	15.5	63
1- 8-70 *	2942	3614	4.5	48
3- 5-70	2896	3508	13.5	61
5-12-70	2949	3389	12.0	57
7-14-70	2284	2910	11.4	68

* = periods when lavage was carried out.
VC = vital capacity.
TLC = total lung capacity.
DLCO = diffusing capacity of the lung for carbon monoxide.
P_{O_2} = oxygen partial pressure.

DR. PHILLIPS: The data (Table 1) after February 16, 1968 were after lavage. The values remained fairly constant but there was a slight improvement in the diffusing capacity of the lung for carbon monoxide (DLCO) but this falls within the range of error of the method.

NORMAN J. LEWISTON, MD:* *Was not the loss of surfactant quite acute?*

DR. ROBIN: What happens acutely after a lavage depends on the balance between lung damage acutely produced by lavage versus how much intraalveolar clearing occurs. I think it is an error to consider lung damage produced by lavage as simple loss of pulmonary surfactant since atelectasis does not develop in most people in whom lavage is carried out. If the lung is filled with isotonic saline, there is swelling of mitochondria and changes in alveolar epithelium for about 48 to 72 hours after filling of the lung. (Incidentally, one wonders about investigations based on obtaining human alveolar macrophages from normal volunteers by carrying out lavage of their lungs. There is no question that reversible lung damage is produced for 48 to 72 hours.) In some patients, especially those with acute forms of alveolar proteinosis, the response may be a quick increase in P_{O_2} but there are patients in whom P_{O_2} is decreased or unchanged for variable periods. Some of them may improve after the postlavage period, theoretically because the damage that has been produced in relatively normal lung segments has been reversed and because oxygen exchange has been improved. Unfortunately, in some patients, lavage produces no improvement at all.

*Assistant Professor of Pediatrics.

DR. LYNNE-DAVIES: *Why does mitochondrial swelling occur with isotonic saline washings?*

DR. ROBIN: Although one mechanism for mitochondrial damage is osmotic injury, it is not the only mechanism. I suppose that changes in sodium and chloride concentrations, in the cell cytoplasm and other factors associated with saline instillation can produce structural and ultrastructural alterations in various lung cells and their mitochondria.

DR. LASURE: The alveolar epithelial cells probably get some of their oxygen supply directly from the inspired gas and lavage may lead to impairment of oxygen exchange.

DR. PHILLIPS: *In 1969 you suggested* SSKI *as therapy, Dr. Robin; can you give us some background about that suggestion?*

DR. ROBIN: Let me say several things about that. By coincidence *The New England Journal of Medicine,* in August 1974, contained a clinicopathologic conference about a patient with pulmonary alveolar disease who was treated with SSKI.[5]

Dr. Castleman, who is the retired chief of pathology at the Massachusetts General Hospital, says in the article: "Many years ago at the Peter Bent Brigham Hospital, there was a patient who was admitted in a very critical condition with similar pulmonary changes [meaning proteinosis]. Very little improvement occurred, and she returned to her home, where her physician instituted potassium iodide therapy. In one year pulmonary-function values and radiologic findings returned to normal, exactly as happened to this patient, and it was assumed that the potassium iodide was responsible for it."

The patient was actually a patient of mine in whom proteinosis developed two years before proteinosis was first described by Rosen, Castleman and Liebow. She was a 16-year-old girl in whom the diagnosis of "Pneumocystis carinii" had been made because of lung biopsy findings. The pulmonary function and pathologic findings of these two diseases are virtually indistinguishable except that Pneumocystis is found in pneumocystis pneumonia and not in proteinosis. She was indeed very critically ill. This case taught me to be very

TABLE 2.—*Classification of Pulmonary Alveolar Proteinosis (PAP)*

1. Primary (Idiopathic) Pulmonary Alveolar Proteinosis
2. Secondary Pulmonary Alveolar Proteinosis
   a. Alkylater lung
   b. Pneumocystis carinii
   c. Fungal infection
      Cryptococcosis
      Nocardia
   d. PAP associated with hematologic disorders
   e. Acute silicosis

careful in providing prognostic information to patients and their families. The Po_2 was in the 40's and both of the lung fields were filled with homogeneous ground glass densities. Her father insisted that he wanted to know exactly what was going on. When I said that as far as we knew, she had a fatal lung disease, he promptly fainted. I had misjudged his desire to be informed.

We prescribed potassium iodide because at that time SSKI was considered to be a good sputum liquifier. I wrote the prescription for 15 drops three times a day which was standard therapy and somehow there was an error and she was given 60 drops three times a day. She went home, I thought to die, and six weeks later, I received a letter from her father stating that the medicine was working well and his daughter was improving. We had the patient return and indeed in about six weeks about half of the abnormal densities seen on x-ray films were gone. The Po_2 had gone from 40 to 65. Over the next two or three months, the disease completely regressed. We continued administration of SSKI. We maintained communication and I successively received invitations to her high school graduation, her college graduation and her wedding. The patient has not received potassium iodide for many years now. It is now apparent that there are spontaneous regressions in patients with PAP. It appears that at least 50 percent of patients with proteinosis have complete remissions and probably 75 percent of patients with proteinosis have partial remissions so that the iodides may have had nothing to do with the remission.

One of the interesting leads to the pathogenesis of pulmonary alveolar proteinosis is that lung sections from these patients show few pulmonary alveolar macrophages in affected areas. When we started working on isolated alveolar macrophages, we looked for these cells in the fluid in the lavage fluid in proteinosis. There were almost none found. We collected some of the lavaged material from one of our patients. We divided this material into two aliquots. One aliquot was treated with iodide and the other was not treated. We added rabbit alveolar macrophages to both groups of material. The macrophages phagocytosed the material to which iodide had been added but there was no ingestion of noniodide-treated material. This was a single uncontrolled and undisciplined experiment. Since I am convinced that the indications for lavage are much more limited than those claimed by Ramirez, we have not had the opportunity to repeat these studies. We speculated that iodide might iodinate phospolipids *in situ* in the lung and thus attract macrophages which would then ingest the material.

On the basis of this tenuous and uncertain scientific information, if I were given a patient with PAP who was doing very poorly, I would give him a trial on iodides. Even if the possibility that iodides are helpful is not all that high, the possibility of the harm is very small and conceivably this drug may be therapeutically useful.

One interesting aspect of proteinosis is that primary or idiopathic proteinosis (see below) seems to be disappearing. Another puzzle is that when Rosen, Castleman and Liebow went back over pathologic material before 1958, they did not find a disease state that could definitely be called alveolar proteinosis before 1958. A plot of time versus incidence might show limited incidence before 1958 to a peak incidence around 1958 to 1965 and since that time, a decreasing incidence. The number of cases on which this concept is based is very small. Dr. Liebow would probably interpret this curve as showing that there must have been some kind of peculiar infection or some kind of environmental pollutant which peaked around the late 1950's and early 1960's and is now disappearing. Incidentally the geographical distribution is also very interesting because in Asia and Australia the incidence of proteinosis is much smaller than in other areas.

One important question concerning this disease is whether it represents a single etiologic entity. There is now evidence that PAP is not a single disease. Table 2 presents a classification based on the view that PAP is not a single entity. One form of PAP is unassociated with other diseases and might be considered as primary or idiopathic PAP because of lack of associated disease. This is the form present in our patient. Secondary PAP are disorders with typical changes in the lung, but associated with a variety of other diseases. One

disorder which shows this relationship is "alkylater" lung. In patients being treated with busulfan or other alkylating agents, localized areas of PAP may be seen along with interstitial abnormalities, cellular infiltration and pulmonary fibrosis.[6] Pneumocystis carinii infestation of the lung is another disease in which alveoli are filled with an amorphous, eosinophilic, periodic acid Schiff (PAS) positive material.[7] In many areas, the specific infectious agent can be identified but in other areas it may not be possible to find pneumocystis. The mechanism by which infection with pneumocystis leads to the filling of alveoli with cellular debris is not at all clear. Various fungal infections like Cryptococcus and Nocardia may show areas in the lung with a picture indistinguishable from that of PAP.[1,2] In patients with a variety of hematologic disorders (neutropenia, aplastic anemia) typical findings of PAP may be present in the lung.[8] Finally, acute silicosis has been reported to be associated with the development of PAP.[9]

Recent biochemical studies add important dimensions to our knowledge of the pathogenesis of PAP.[10] The amorphous PAS positive material, which is insoluble in saline, has been removed by lavage and analyzed chemically. This material contains substantial amounts of phospholipids including dipalmitoyl phosphatidyl choline, an important component of the surfactant system. There are also significant amounts of two hydroxyproline containing glycoproteins. Both the phospholipids and particularly the glycoproteins are found in the lamellar bodies of alveolar Type II epithelial cells. The lamellar bodies appear to be the site of storage of surface active material which is synthesized in the Type II cells. It has been suggested that the glycoproteins are uniquely found only in Type II cells and therefore represent a marker for this cell. It is therefore reasonable to suggest that the origin of the material which fills the intraalveolar spaces is from broken-down Type II alveolar epithelial cells and that PAP represents an abnormality of this cell type. Under some circumstances, this basic abnormality could be an increased rate of breakdown of Type II cells. In other circumstances, the basic abnormality could be decreased rate of removal of broken-down Type II cells—say by altered macrophage function.

DR. LYNNE-DAVIS: When I was junior resident, we had a patient with severe bilateral bronchiectasis in whom amyloid subsequently developed —we thought amyloid of the lung. When he died, alveolar proteinosis in the lungs was found and amyloid every place else. It was as though he had responded with two rather nonspecific responses to possibly one underlying cause.

QUESTION FROM THE AUDIENCE: *What is the connection between* PAP *and desquamative interstitial pneumonia,* DIP?

DR. ROBIN: PAP and DIP are both disorders associated with intraalveolar filling and in which interstitial involvement is minimal or absent. In DIP, the alveoli are filled with intact (perhaps Type II) cells. Some workers feel that DIP is a specific disease. Others feel that intraalveolar cellular desquamation is an integral part of many different types of interstitial disease. DIP tends to respond favorably to steroid therapy. It has been suggested that the presence of extensive intraalveolar cellular desquamation found on lung biopsy indicates a high probability of a favorable response to steroid treatment.

DR. THEODORE: When Ramirez and his group in Maryland analyzed the composition of the proteinosis material, they found it very similar to pulmonary surfactant but without surface-active properties.[4] They proposed the disease as an abnormality of surfactant clearance. You either have an over-synthesis or an under-clearance of this material. Dr. Robin has already suggested macrophage dysfunction as one of the key features in proteinosis.

DR. ROBIN: The material does have surface-active properties. The difference between this material and normal surfactant turns out to be quantitative and not qualitative. The art of quantitating the surface-active material obtained by lung washout is very complex, and I do not regard the Maryland work as necessarily convincing.

DR. THEODORE: They used this work as evidence for the need for lavage in that they were postulating a defect in clearance. The recent data with high percentages of partial and complete remission put big holes in their theory unless you postulate a transient problem.

DR. LEWISTON: *What physiologic changes occur during pulmonary lavage?*

DR. ROBIN: The hydrodynamics of lung lavage are very interesting. We did studies which were published in *Anesthesiology.*[11] These were carried

out by a young anesthesiologist named Jan Smith who was working with us. During lavage, a column of fluid is introduced at a pressure greater than atmospheric. We measured central venous pressure (CVP), pulmonary capillary, left atrial, left ventricular end-diastolic and right ventricular end-diastolic pressures. We were infusing a large amount of saline and I wondered if we should monitor CVP to guard against congestive heart failure. We noticed that venous pressure rose after we had introduced the fluid and I thought we had caused fluid overload even with a small amount of salt. The venous pressure fell when we drained out the fluid by lowering the bottle. What we had done was to introduce a fluid column into the chest. All of the intrathoracic structures were subjected to the increased hydrostatic pressure so central venous pressure and all other intrathoracic pressure increased.

We also wondered about what would happen to blood flow to the lung which had had a pronounced increase in intraalveolar pressure. Since capillaries are distensible units and water has more weight than air, increased intraalveolar pressure will be present in areas in the lung which are filled with saline. This, in turn, should cause a loss of perfusion to these areas. To prove this, we did a simple experiment. When the lung was filled with liquid, arterial Po_2 was high and when it was emptied, arterial Po_2 would fall. When the lung was filled, it was no longer operating as a shunt because perfusion had been knocked out by the weight of the water. When the water is drained out, perfusion returns and these areas act as shunts. This shows that pulmonary capillaries are distensible and are exposed to intraalveolar pressure.

DR. LYNNE-DAVIES: *Did you have an incidence of hydrothorax with lavage?*

DR. ROBIN: No and I do not think you should, because transmission of the pressure throughout the thorax is more or less equal. What would really rupture vessels would be a change in pressure. We did not measure pleural pressures but we did measure esophageal pressures and these were also raised. What we have done is the opposite of being immersed in deep water. With immersion, there is a pronounced increase of negative pressure by having a more positive pressure on the outside. This does not change hemodynamic factors, or transmural factors and there need be no change in blood flow.

My present conception of this disease is first of all, that it is not a single disease but has primary and secondary forms. The incidence of the primary form may be decreasing. One of the pathogenetic mechanisms may be an inability of normal macrophages to be attracted to this material once it is deposited intraalveolarly. It should not be considered a terrible and invariably fatal disease. Most of the patients experience remissions, so that it is difficult to evaluate therapeutic approaches. There is good evidence that lavage in many patients is unnecessary although an acutely ill patient with a very low Po_2 who is not responding may benefit from lavage. There appears to be an acute, a subacute and a chronic form of the idiopathic form of proteinosis. One of the major dangers to these patients is the possibility of secondary infection, particularly by fungal disease. They clearly should not be treated with steroids.

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Refer to: The clinical pharmacology of lidocaine as an antiarrhythmic drug—Medical Staff Conference, University of California, San Francisco. West J Med 124:36-43, Jan 1976

The Clinical Pharmacology of Lidocaine as an Antiarrhythmic Drug

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *It has been our custom at the end of each academic year to ask the incumbent chief medical residents to speak at Medical Grand Rounds. It offers us a chance to thank them publicly for their participation in our academic program during the year. Ken Collinsworth has entered the navy and is serving as staff cardiologist at Oak Knoll Naval Hospital. He has returned today to speak on the clinical pharmacology of lidocaine as an antiarrhythmic drug. I want to express my personal appreciation for the distinguished way in which he served as chief medical resident in the Department of Medicine during this past year.*

DR. COLLINSWORTH:† Thank you, Dr. Smith. Today, I plan to discuss the clinical pharmacology of lidocaine and some aspects of its use. First, I will briefly describe the chemistry and metabolism of lidocaine.[1] The chemical structure of lidocaine is one of an aromatic group, 2,6-xylidine, to which is coupled diethylglycine by an amide bond. It is metabolized chiefly by the liver, and the major pathway of degradation as illustrated in Figure 1 appears to be conversion to monoethylglycylxylidide, to 2,6-xylidine and finally to 4-hydroxy-2,6-xylidine. These and various other metabolites are excreted in the urine. In addition, a small percentage of unchanged lidocaine, up to 10 percent, is also excreted in the urine. The major metabolic end product is 4-hydroxy-2,6-xylidine since up to 70 percent of an administered dose of lidocaine appears as this compound in the urine. The cyclic form has now been recognized to be the result of laboratory artifact and is not a usual metabolite, and the N-hydroxy forms are now considered not to occur in humans.

It is useful to review the electrophysiologic effects of lidocaine as a background for understanding its antiarrhythmic actions. Applying experimental results to clinical medicine is risky and especially so with lidocaine. The electrophysiologic studies have been carried out mostly in isolated heart preparations using different parts of the myocardium from a variety of different animal species with the attendant possibility of species

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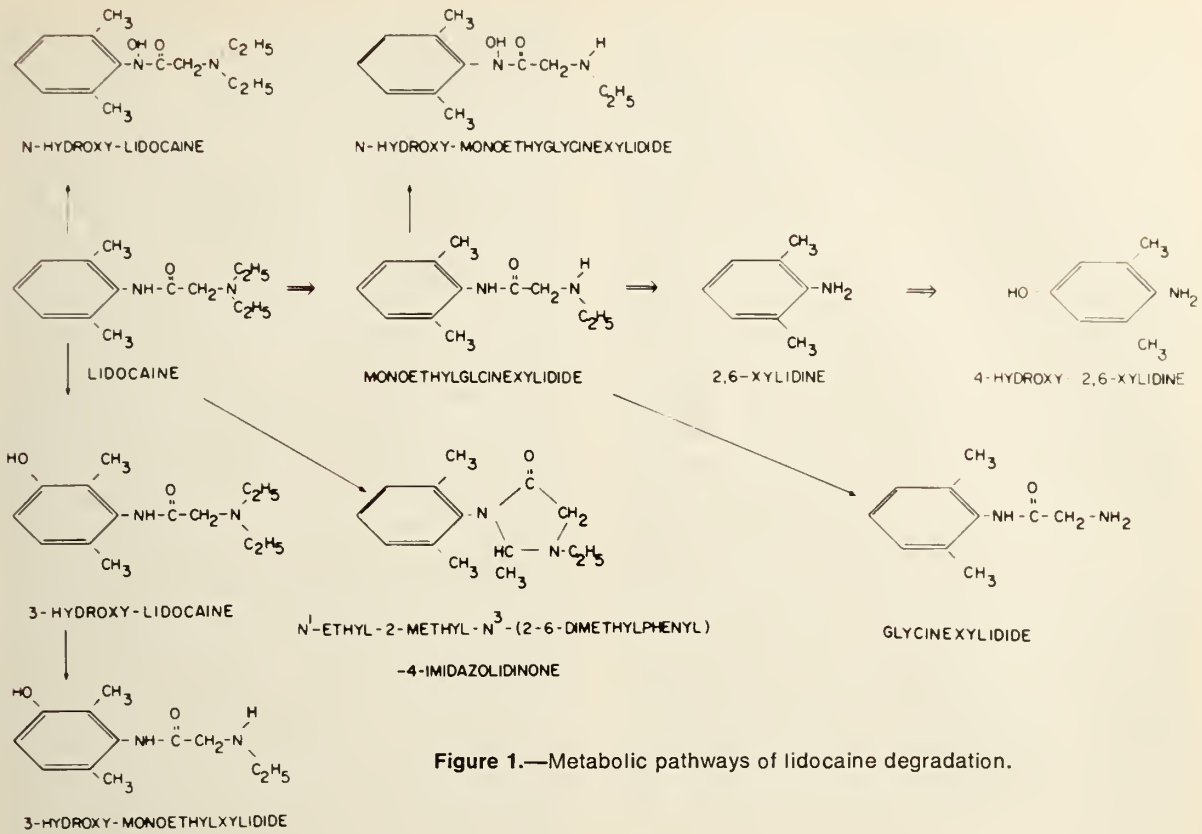

Figure 1.—Metabolic pathways of lidocaine degradation.

and tissue variation. Most of these studies have been done with presumably normal, undamaged myocardium, in well oxygenated tissue baths but without the microvasculature perfused. Various potassium concentrations have been present in the bathing media. Because of these variations in study technique many of the resulting data are conflicting. To extrapolate these data to explain why lidocaine suppresses the cardiac arrhythmias in humans in the setting of acutely ischemic or infarcted hearts possessing intact autonomic nervous systems with various degrees of activity, must be considered purely speculative. Nevertheless, a common consensus of the electrophysiologic actions of lidocaine seems to be emerging from the literature.[1,2a,2b]

In Figure 2, an idealized monophasic action potential from a Purkinje fiber is depicted. The normal action potential is represented by the solid line, while the dashed line represents the action potential after lidocaine is present in the tissue bath at a concentration which would be equivalent to a therapeutic dose of lidocaine in humans. The rate of spontaneous depolarization (phase 4) which accounts for the automaticity of pacemaker tissue, appears to be decreased by therapeutic levels of lidocaine. The duration of the action potential is decreased, but perhaps more important, the effective refractory period (during which time the fiber is unresponsive to stimuli) is not comparably shortened. Therefore, the Purkinje fiber is inexcitable for a greater fraction of the depolarization-repolarization cycle.

The maximal rate of depolarization of the

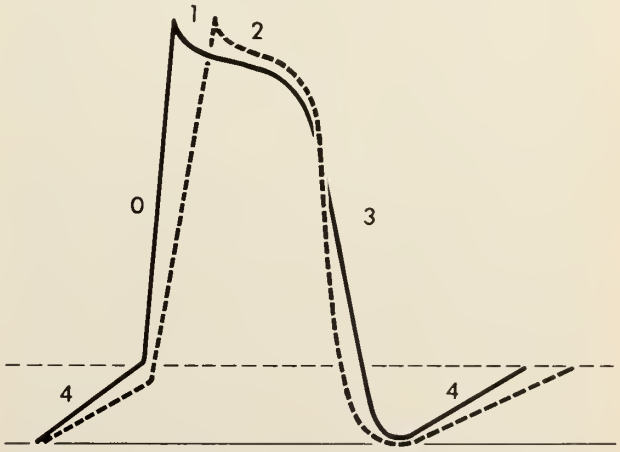

Figure 2.—Monophasic action potential of Purkinje cell. Solid line represents normal action potential. Dashed line represents action potential after lidocaine present.

action potential during the phase 0 period is controversial. Bigger's studies[2a] have shown that the maximum rate of depolarization is accelerated by lidocaine, whereas Singh and Williams[2b] have shown that the maximum rate of depolarization is decreased by lidocaine. The conflicting results probably are due to the different potassium concentrations used in the tissue baths since potassium can influence the transmembrane potential and thus the rate of depolarization. I personally believe that the evidence is in favor of lidocaine slowing phase 0; however, this effect appears to be much less than that induced by procainamide or quinidine. The conduction velocity in Purkinje fibers appears to be decreased slightly, consistent with a decreased maximal rate of depolarization. It has also been shown that the fibrillation threshold is increased by lidocaine, that is, more current must be applied to induce the tissue to fibrillate during the vulnerable period of the cardiac cycle. At therapeutic concentrations of lidocaine, the Purkinje system appears electrophysiologically to be most affected, with lesser effect produced on the ventricular muscle and still less effect on the sinus and atrioventricular (AV) nodes and atrial muscle.

The two major theories of the cause of ventricular arrhythmias are: (1) enhanced automaticity by Purkinje pacemaker tissues in the ventricle and (2) reentry due to slowed or decremental conduction through ischemic or damaged myocardium. As to arrhythmias caused by increased automaticity of pacemaker tissue in the ventricle, lidocaine may well have its antiarrhythmic effect by suppressing the phase 4 spontaneous depolarization and, therefore, suppressing the automaticity. The reentrant arrhythmias, on the other hand, may be suppressed by lidocaine's effect on altering conduction velocity and action potential, in this way interfering with the reentrant pathway.

We can now discuss the antiarrhythmic uses of lidocaine. Lidocaine has been shown to abolish or to decrease ventricular premature beats and to terminate ventricular tachycardia occurring in a variety of clinical situations. It has been shown to be effective during general surgical procedures, during cardiac surgical operation, after acute myocardial infarction and in the presence of stable ventricular premature beats occurring in a variety of cardiac diseases—including coronary artery disease and cardiomyopathies. It has been effectively used in the presence of digitalis intoxication. In patients with acute myocardial infarctions in a coronary care unit, it has been shown that in approximately 80 percent ventricular premature beats will be abolished or decreased by lidocaine.[3]

Several controversies remain concerning the use of lidocaine in acute infarction, however. Several reports indicate that in the first one or two hours following the appearance of the symptoms of infarction, administration of lidocaine is much less effective treatment for ventricular premature beats than it is after several hours following the onset of symptoms. One article reported a series of patients with acute myocardial infarction treated with lidocaine within four hours of the onset of symptoms.[4] In 30 percent of patients ventricular premature beats were abolished, in 19 percent they were decreased and in 20 percent there was no effect. It is interesting that in 19 percent there actually was an increase in the number of ventricular premature beats shortly after lidocaine was administered and occasionally even ventricular tachycardia developed. There are animal studies which also show enhancement of ventricular premature beats following lidocaine administration in the early stages of experimental infarction. The usefulness of antiarrhythmic agents in the earlier stages of infarction is important since approximately two thirds of the deaths from acute myocardial infarction which are believed to be due mostly to ventricular fibrillation occur during the first hour after the onset of symptoms.[5]

The cause for apparent insensitivity to lidocaine during early acute infarction is not known. Some investigators feel that the mechanism producing arrhythmias during early acute infarction differs from that occurring later in the course of infarction.[6] Adrenalin and sympathetic nervous system activity may be notably increased in early acute infarction causing the ventricular premature beats. There is a small clinical experience in patients with infarctions to suggest that practolol, a beta adrenergic blocking agent, is effective in treating the acute phase ventricular premature beats but not the later stage ventricular premature beats. There is also some evidence from experimental infarctions in animals to suggest that adrenalin may play an important role in the genesis of ventricular premature beats that are responsive to beta adrenergic blockers but not to lidocaine. One study recently reviewed the results of administering lidocaine intramuscularly to one large group

of patients in doses known to produce therapeutic blood levels, and a placebo to a second large group of patients when first seen in the prehospital phase for symptoms suggesting acute infarction.[7] Of those who ultimately were shown to have had infarctions, the lidocaine treated group had a slightly, but significantly, lower incidence of early mortality. The late mortalities were not different in the treated and the untreated groups after entering the coronary care unit and were usually due to pump failure.

Another controversy exists as to whether prophylactic lidocaine should be given to prevent ventricular fibrillation in all patients with acute infarction as they enter the coronary care unit. The rationale has been that ventricular fibrillation in acute infarction is usually preceded by a premonitory ventricular arrhythmia. The usual indications for administering lidocaine to patients with acute infarction are the following: (1) when more than five ventricular premature beats of unifocal origin occur per minute; (2) when the R waves of premature ventricular beats are noted on the T waves of the previous contraction; (3) when multifocal ventricular premature beats occur; (4) when two or more ventricular premature beats occur in sequence, that is to say short bursts of ventricular tachycardia, and (5) during sustained ventricular tachycardia. The feeling has been that primary ventricular fibrillation is likely to follow the types of ventricular arrhythmias just mentioned and suppression of such arrhythmias is indicated. Primary ventricular fibrillation is defined as ventricular fibrillation occurring in the absence of cardiogenic shock or severe congestive heart failure. Several studies have approached this problem and the results are not conclusive. Either a small or no decrease in primary ventricular fibrillation is found when comparing prophylactically lidocaine-treated *versus* placebo-treated groups of patients with acute infarction in a coronary care unit.[8,9] It is of interest that in these studies, which show either some or no decrease in primary ventricular fibrillation, the ultimate mortalities of the treated and the untreated groups with infarction were essentially the same after they entered the coronary care unit, and death was usually due to pump failure or cardiac rupture and not arrhythmias.

My conclusions are the following: (1) prophylactic lidocaine probably should not be given to every patient with suspected or proven acute infarction in the coronary care unit; (2) so-called premonitory arrhythmias should be treated; (3) primary ventricular fibrillation is not a major cause of mortality in the coronary care unit and can be effectively treated by electrical conversion; (4) pump failure and cardiac rupture are the major causes of death in the coronary care unit. The conclusions that I have drawn from the studies about lidocaine in patients with acute infarction before their admission to hospital are that if ventricular arrhythmias are present in a patient with suspected acute infarction when first seen at home or generally before entering the hospital, he or she should be given intramuscular lidocaine. Lidocaine in a dosage of 300 mg administered into the deltoid muscle will provide therapeutic blood levels. In the absence of ventricular arrhythmias or in the presence of bradycardia or hypotension, lidocaine should not be given without adequate monitoring. The reasons are that ventricular fibrillation in a coronary care unit can be treated effectively with electrical conversion but such treatment may not be possible in the prehospital phase, and lidocaine may just provide the necessary antiarrhythmic protection even though its efficacy may be less in the first two hours after infarction.

Lidocaine has not been effective in certain cardiac arrhythmias: (1) it has not been very effective in terminating ventricular fibrillation after it has already begun; (2) it has generally not been effective in terminating supraventricular arrhythmias. It might be reasoned that this would be the case since experimentally the action potential in atrial muscle, sinus nodal or AV nodal tissue is, as mentioned above, little altered by lidocaine.

It has been found that blood levels above 1.2 micrograms (μg) per ml are therapeutic, the therapeutic range being defined as between 1.2 and 5.0 μg per ml over which range there was in 80 percent of patients with ventricular premature beats suppression or a significant decrease in ventricular ectopy.[3] A dose response relationship was defined, such that for any given patient, ventricular premature beats were progressively suppressed as the blood level increased. The toxic range has been defined as being greater than 5 μg per ml. In the 5 to 9 μg per ml range, toxicity will be seen in a few patients. Above 9 μg per ml at least some manifestations of toxicity will be seen in most patients.

I will now turn to a discussion of the pharmacokinetics of lidocaine. First, the blood level of lidocaine following an intravenous bolus can be

depicted by a biphasic curve, as shown in Figure 3. Initially the blood level falls rapidly with a half-life of approximately ten minutes. This is mainly due to drug mixing and distribution to the peripheral tissues. A second, delayed fall then appears with a half-life of about two hours and follows first order kinetics. This is mainly due to clearance by the liver. Because mixing and distribution occur rapidly during constant intravenous infusion, the value of a slower half-life of about two hours should be used in determining dosages and blood levels. Using the half-life value of two hours, a constant infusion then takes about six hours to attain 90 percent of the steady state levels and up to about ten hours before steady state levels are actually reached. After discontinuing an infusion at steady state levels, the half-life of blood level is the same as the slower second curve, that is, about two hours.

In treating arrhythmias, understanding the pharmacokinetics of lidocaine is important. First,

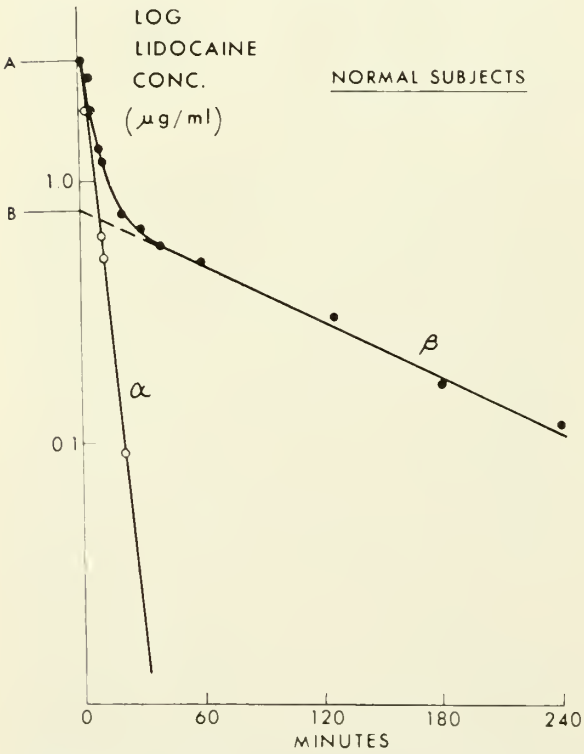

Figure 3.—A biphasic curve following a single intravenous bolus of 50 mg of lidocaine. A and B are the zero time intercepts of data plotted on semilogarithmic paper, while α and β are the rapid and slow time constants, respectively. The closed circles represent observed data, whereas open circles represent derived data. (Reprinted with permission of Thomson PD, et al and Am Heart J: The influence of heart failure, liver disease, and renal failure on the disposition of lidocaine in man. Am Heart J 82:417, 1971)

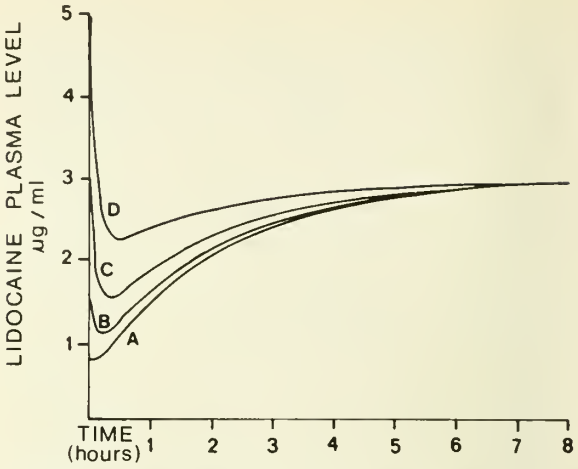

Figure 4.—Calculated lidocaine plasma level curves where a 4 mg per minute infusion has been combined with a 40 (A), 80 (B), 160 (C) and 320 (D) mg rapid intravenous dose. (Reprinted with permission of Boyes and Keenaghan[15]).

an intravenous bolus will rapidly provide blood levels in the therapeutic range and suppress arrhythmias, but since the blood levels fall very rapidly, arrhythmias often return within 15 to 20 minutes. Therefore, intravenous bolus administration alone is not a practical way to treat a persistent arrhythmia. On the other hand, a constant infusion alone may take two or three hours at a minimum before therapeutic levels are achieved and the arrhythmia suppressed. Constant infusion alone then is not a practical way to treat a serious acute arrhythmia. Both intravenous bolus and constant infusion are combined in order to provide therapeutic blood levels at all times after beginning therapy. Figure 4 shows the resultant blood level curves of different initial bolus doses but with the same constant infusion rate. A minimum level is reached at about 30 minutes followed by a slow rise to steady state levels. At the lowest point the blood level may drop below the therapeutic range and arrhythmias may break through. If this occurs, a small bolus dose of perhaps a quarter to a half of the initial bolus can be given slowly to increase the blood level until the constant infusion raises the blood level above the minimum therapeutic level.

It is important to choose the correct dosage, both for the intravenous bolus and the constant infusion rate, to achieve adequate therapeutic blood levels without pushing them into the toxic range. To do this requires an understanding of the pharmacokinetics of lidocaine. Clearance of lidocaine is mainly by hepatic metabolism which is very rapid, such that the actual rate of clearance de-

TABLE 1.—*Dosage Recommendations*

Normal cardiac output and liver function
150 mg bolus, 4 mg per minute infusion
Mild-moderate decreased cardiac output or liver disease
100 mg bolus, 2-3 mg per minute infusion
Notably decreased cardiac output or shock
50 mg bolus, 1 mg per minute or less infusion

pends upon hepatic blood flow. In patients with reduced cardiac output and congestive heart failure, whether it is acute or chronic, the hepatic blood flow, which is proportional to cardiac output, and the drug clearance are decreased such that any given rate of lidocaine infusion will result in higher blood levels. In patients with liver failure, hepatic clearance may also be reduced though there tends to be much variability in the degree of reduction. In addition, in patients with congestive heart failure there is decreased volume of distribution of lidocaine presumably because of diminished perfusion to the peripheral tissues. This also leads to increased blood levels at any given infusion rate. These concepts of pharmacokinetics are well covered in recent articles.[10,11]

Using this information and clinical experience, dosage recommendations for lidocaine administration can be made.[1] The dosages given in Table 1 are for a man weighing 70 kilograms and it must be realized that a weight adjustment must be made since the volume of distribution also depends on the size of the patient. These dosages have been worked out to provide effective therapeutic levels at all times after the initiation of bolus. In patients with normal cardiac output and liver function, a 150 mg bolus followed by a 4 mg per minute infusion will provide therapeutic levels. It is probably not likely that lidocaine will be administered at dosages this high because most patients requiring lidocaine do have cardiac disease and many of them will have diminished cardiac output. The next dosage recommendation range is for those with a mildly to moderately decreased cardiac output, or those with liver disease. A 100 mg bolus followed by a 2 to 3 mg per minute infusion will provide therapeutic blood levels. Whether it be a 2 or 3 mg per minute infusion would depend upon clinical judgment as to the patient's cardiac output. Finally, in patients with notably decreased cardiac output, or those who are in shock, no more than a 50 mg bolus followed by a 1 mg per minute infusion is recommended; and in certain instances these dosages may well be excessive. In patients who are in shock, for example, liver blood flow and clearance of lidocaine may be severely reduced, such that even small dosages may rapidly lead to toxic blood levels. Intramuscular injection will also provide therapeutic blood levels that are effective in treating arrhythmias. A dosage of 300 mg of lidocaine administered as a 10 percent solution in the deltoid muscle will provide therapeutic blood levels in about 10 to 15 minutes persisting for at least an hour. Intramuscularly given lidocaine may have a place in treating arrhythmias in patients with acute infarctions seen before they get to the hospital. Orally administered lidocaine does not provide effective blood levels because it is mostly removed from the portal blood by the liver before it reaches the systemic circulation.

When giving lidocaine, administer the intravenous bolus slowly, at least over one or two minutes. Too rapid an administration is probably the most common cause for lidocaine toxicity. An immediate injection leads to extremely high blood levels since at least a few minutes are needed for dilution and distribution of the drug. Commonly, however, lidocaine is rapidly administered as an all-at-once bolus, and it is not surprising that patients complain of dizziness or other toxic symptoms following such rapid injection. With regard to constant infusion, it is certainly possible to attain therapeutic blood levels quite rapidly using a higher than usual rate of infusion, such as 6 to 8 mg per minute, but the ultimate steady state levels are certainly going to be in the toxic range since the clearance rate of the drug will not change and the higher the infusion rate the higher the resultant steady state level. A patient with moderately severe congestive heart failure may do well for the first several hours on a 4 mg per minute infusion and arrhythmias may be controlled, but sometime later in the day the blood levels very likely will be in the toxic range. Understanding the half-life principle is important for adjusting an ongoing, constant infusion rate. If arrhythmias develop while constant infusion is being carried out, and a higher blood level is desired to see whether that will control the arrhythmia, turning up the infusion rate from 2 to 3 mg per minute will require perhaps an hour before the blood level has substantially increased. In this situation small bolus doses of 10 to 25 mg may be given slowly and repeated every 20 to 30 minutes, or at briefer intervals. This should increase the blood level substantially without resulting in toxic levels. If blood levels during constant in-

fusion are recognized as being toxic, it must be understood that after stopping the infusion the toxic symptoms may persist for some time, since approximately two hours will pass before the blood level decreases to 50 percent of the blood level at the termination of the infusion. If lidocaine blood level assay is rapidly available, such a determination may be helpful for adjusting the rate of infusion.

I now will discuss some aspects of the side effects and toxicity of lidocaine. Central nervous system (CNS) toxicity is the most common side effect of lidocaine and is the result of excessive blood levels, as mentioned earlier. Blood levels from 5 to 9 μg per ml are associated with occasional side effects and blood levels greater than 9 μg per ml are commonly associated with CNS side effects. The milder signs of CNS toxicity include dizziness, drowsiness, paresthesias, disorientation, agitation, twitching, double vision and diminished hearing. Severe side effects include seizures and respiratory arrest. Almost all instances of CNS toxicity represent clear-cut overdosages. Immediately after an intravenous bolus given too quickly, very high blood levels appear and since brain and blood lidocaine levels equilibrate quickly, very high brain levels result and lead to toxic effects. Fortunately, after an intravenous bolus the blood and thus brain levels decrease within minutes and symptoms of CNS toxicity diminish rapidly. This sequence is probably the most common example of lidocaine toxicity. If CNS toxicity occurs during constant infusion, the blood and the CNS symptoms take longer to decrease. Seizures do respond well to small doses of intravenous diazepam. The contribution of the metabolic products of lidocaine degradation to toxic effects is not clear at this time. Two of the major metabolites, monoethylglycylxylidide and glycylxylidide, may, however, be responsible for CNS toxicity in some cases, and some documentation exists for this in humans during constant infusion.[12] In animals monoethylglycylxylidide can clearly induce convulsive activity equivalent to that of lidocaine. Also, in animals the convulsive effects of lidocaine are added to that of its metabolites.

I would now like to review the cardiac side effects. When delivered in a way that results in therapeutic blood levels,[1] lidocaine appears to cause no or minimal decrease in cardiac pump function as measured by ventricular contractility, cardiac output, arterial pressure or heart rates in normal humans, in patients with chronic cardiac disease and in patients with acute infarction. Overdosage, however, can clearly cause hypotension, likely due to a direct depressant effect on the myocardial contractility, especially in a damaged heart. This again usually occurs when an intravenous bolus is injected much too rapidly resulting in high blood levels but, fortunately, usually is also transient. In pacemaker tissue, subsidiary pacemaker tissues (such as those in the Purkinje system) seem to be suppressed more than sinus or junctional tissues. Findings in most human and animal studies support this statement and show minimal changes in the sinus or junctional rates after administering therapeutic doses of lidocaine. This generalization would appear to apply to patients with normal hearts, patients with chronic heart disease and patients with acute infarctions. This generalization would also include those patients with acute infarction with sinus bradycardia.[13] However, there are numerous published case reports and many anecdotes about sinus bradycardia, sinus arrest or junctional rhythm depression developing in patients after intravenous administration of lidocaine. Most of these instances again appear to be due to overdosages, are usually transient and are usually associated with CNS toxicity following too rapidly administered lidocaine. Yet, there are a few reports, usually in the setting of the sick sinus syndrome and in acute infarction, in which sinus slowing or arrest has resulted from apparently appropriately administered doses of lidocaine. Thus, caution must clearly be used when sinus dysfunction, atrioventricular block or junctional rhythm is present. However, in most cases, lidocaine administration may be safely used.

Results of His's bundle studies have shown that lidocaine may be safely used in patients with chronic intraventricular conducting defects (such as right bundle-branch block, left bundle-branch block or with atrioventricular nodal delay) without increasing the block at lidocaine blood levels which are considered therapeutic and were effective in abolishing arrhythmias.[14] Again, these were patients with chronic conduction defects, not patients with recent infarction or congestive heart failure. There are isolated reports in the literature citing examples of various degrees of increased heart block following lidocaine administration, mostly in patients with acute infarction. Again, in most of these reports lidocaine bolus overdosage appears to have been the cause of the

heart block. However, there remain a few instances of heart block that have been shown to follow apparently appropriate doses of lidocaine. The message, then, is the same as that concerning pacemaker tissue suppression. Lidocaine in appropriate doses is generally safe in treating patients with conduction disturbances, but caution must be used particularly with the rate of bolus administration.

To conclude, I will comment on allergic reactions. We always ask our patients about local anesthetic reactions before administering lidocaine and consider cross-reactions. However, the actual documentation of true allergic reactions to lidocaine (whether anaphylactic reactions, skin rashes or angioedema) is extremely rare in the literature, but there are a few well documented reports on the subject. In addition, patients with allergic reactions to other local "caine" anesthetics probably do not manifest cross allergy to lidocaine; this appears to be true at least for procaine hydrochloride (Novocain®).

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Important Advances in Clinical Medicine

Epitomes of Progress—Pediatrics

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Pediatrics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Pediatrics which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pediatrics of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Progress Toward Eradication of Smallpox

RECENT NEWSPAPER and television news reports of smallpox epidemics in India have caused apprehension regarding the feasibility of total global smallpox eradication. A brief appraisal of the present situation seems appropriate.

In 1967 the World Health Organization's intensified Smallpox Eradication Program was formally inaugurated; the goal was total worldwide elimination of smallpox within ten years. At that time, although reported disease incidence was incomplete, endemic disease was known to be present in more than 30 countries and in 10 additional countries smallpox had been imported during that year. By the end of 1973, some six years later, the total eradication of smallpox had been achieved in the Americas (in 1971) and in Indonesia (in January of 1972).

Relatively few cases are occurring in Ethiopia, the only African nation with continuing smallpox transmission. Helicopter transport has been used recently to reach remote villages and nomadic groups. Based on current reports, this country should be free of smallpox by late 1975.

The fourth and final region, consisting of three countries of the Indian subcontinent, India, Pakistan and Bangladesh, accounted for 96 percent of all cases in 1973, and at least that proportion in 1974. Two thirds of these cases were reported from northern India. The incidence of smallpox in India has decreased dramatically during the early months of 1975, and endemic transmission of smallpox in that country was interrupted in June of 1975. Despite intensive search, no cases have been found in Pakistan since October 1974. The program is moving rapidly in Bangladesh, and the 1,500 national and 60 international staff members working in that country predict the end of smallpox in Bangladesh by the end of 1975.

During the eighth year of the intensified smallpox eradication program, the goal is clearly attainable and well within the ten-year interval

originally estimated to be required. Despite this magnificent accomplishment, vaccination certificates for international travel will be required by many countries for at least two additional years or until formal certification of all countries as smallpox-free has been completed by an international commission.

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New Drugs in the Therapy of Asthma

WITH AN increasing understanding of the molecular basis of the action of many of the more effective agents, the pharmacotherapy of asthma has reached a more rational and specific basis than in the past. In particular, the appreciation of the role of cyclic 3,5 adenosine monophosphate (CAMP), the intracellular hormone which has been shown to cause bronchial relaxation as well as inhibition of chemical mediator release (histamine and slow-reacting substance of anaphylaxis [SRS-A]), has focused new attention on the pharmacologic management of asthma.

Studies have shown that the pharmacologic activities of adrenergic agents are related to their catecholamine structure. It has been shown that the beta-adrenergic stimulant acts as a first messenger, activating the beta-receptor, adenyl cyclase complex. This catalyzes the production of CAMP from adenosine triphosphate (ATP). Theophylline, on the other hand, inhibits phosphodiesterase thus preventing the degradation of CAMP, resulting in an increase in intracellular CAMP levels.

Due to the many shortcomings of the two principal adrenergic agonists (epinephrine and isoproterenol) available for the treatment of asthma, newer beta-adrenergic agonists are in the process of being investigated while some are now available for use. These agents have three major advantages over epinephrine and isoproterenol. They are effective when given orally, have a longer duration of action and seem to be more selective as pure $beta_2$ stimulators, therefore reducing undesirable cardiovascular stimulation. The three compounds which have enjoyed the most widespread attention are metaproterenol—known in Britain as orciprenaline—(Alupent® or Metaprel®), terbutaline (Bricanyl®, Brethine®) and salbutamol (Albuterol®). Metaproternol is now available in both oral and inhalable forms. It appears to be more effective than ephedrine, but still is not completely free of cardiovascular or stimulating side effects. Terbutaline, initially available in only an injectable form, is now also available in an oral form and appears to be more potent than its predecessor, metaproterenol. Salbutomol, although it has been used in Great Britain, is still not approved for use in this country. Results of investigative studies indicate this agent may prove to be the most effective of the three beta-adrenergic agonists discussed. Salbutomol has been a more potent bronchodilator than either metaproterenol or terbutaline in both oral and aerosolized routes. Two other beta-adrenergic bronchodilators being investigated include Berotec® and Salmefamol®.

The use of the prostaglandins PGE_1 and PGE_2 as bronchial relaxants is currently being studied. However, the disadvantages of their short duration of action, upper airway irritation and induction of bronchoconstriction poses yet unsolved problems.

There is some suggestion that alpha-adrenergic blockers such as phentolamine, thymoxamine or dibenamine may have some usefulness in the treatment of asthma. With a demonstration that stimulation of the subepithelial irritant receptors of the tracheobronchial tree initiates a vagal reflex with resultant bronchospasm, there has also been renewed interest in the use of atropine by inhalation and intravenous administration, as a cholinergic inhibitor.

Because of the well known undesirable side effects of systemic corticosteroid therapy, particularly growth suppression, investigation of topically-active agents has received great emphasis. Beclomethasone diproprionate has been extensively studied in the United Kingdom and is undergoing similar trials in this country. Neither growth suppression nor suppression of the hypothalamic-pituitary-adrenal axis seems to occur. One important problem has been the appearance of oral, faucial and laryngeal infection with Monilia. This, however, seems to be more of a problem with adults rather than children. The indications for aerosol steroids probably would be: (1) children, in whom asthma is uncontrolled with cromolyn and other bronchodilators without resorting to steroids; (2) children presently steroid-dependent. The most common dose of

beclomethasone has been 100 micrograms (μg) (two puffs) three or four times daily. Cromolyn sodium prophylaxis has been widely discussed in many publications. It is important that indications for its use, the method of administration and that it should be used only as a prophylactic agent be clear to both physician and patient. It probably should be reemphasized that the drug has no use in the treatment of wheezing episodes. Finally, it should probably also be mentioned that the methyl xanthines have enjoyed a resurgence as a new appreciation of bioavailability and appropriate dosage becomes more widely known. The most widely accepted oral program for the use of theophylline is now 6 to 10 mg per kg of body weight per dose, given every six hours around the clock.

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Reye's Syndrome (Encephalopathy and Fatty Visceral Infiltration)

THIS CLINICOPATHOLOGICAL ENTITY, described by Reye and co-workers in 1963, is now recognized as a common, deadly illness of infants and children. The syndrome consists of a mild prodromal illness, associated with anorexia, and symptoms of an upper respiratory infection. The sudden onset of vomiting is the major sign that a serious disease may be involved, since lethargy, irrational behavior, stupor, convulsions and coma generally follow vomiting within the next 24 hours. On physical examination hyperreflexia is seen, and hypertoxicity is found in a child who may be responsive to voice commands (Stage II coma), unresponsive to all but deep pain stimuli (Stage III) or requires mechanical support for failing respiratory function, variable or weak pulses and hypotension (Stage IV). Generally, most children in Stage IV coma do not recover, whereas persistence of Stage III coma without further deterioration for at least 24 hours is a good prognostic sign.

All children with suspected Reye's syndrome should receive a lumbar puncture (normal results) to rule out infectious causes, and tests for serum glutamic-oxaloacetic transaminase, prothrombin time and blood ammonia. These three measurements of liver function are nearly always abnormal in Reye's syndrome, whereas there is no jaundice or significant hyperbilirubinemia, helping to distinguish this condition from fulminating hepatitis. Hypoglycemia is also present in approximately 50 percent of cases. A percutaneous liver biopsy specimen stained for fat is extremely helpful in establishing the diagnosis.

Treatment is nonspecific, and results difficult to evaluate. Since controlled studies of various regimens are unavailable, individual experience must be a guide to therapy. I believe that supportive treatment (electrolyte and fluid balance, reversal of metabolic acidosis and administration of glucose) is all that is necessary in patients who are in Stage III coma or better. Approximately 80 percent will begin the recovery process within 1 to 2 days after onset of coma. The real problem is a child slipping into Stage IV coma. In such circumstances, exchange blood transfusion is indicated, since 80 percent of such patients will die. It is also helpful to note the *trend* of blood ammonia in Stage III. When ammonia levels are on the rise, deterioration will probably become apparent soon thereafter. Therefore, exchange blood transfusions, perhaps combined with peritoneal dialysis, may be indicated in Stage III coma with rising blood ammonia levels.

The cause of Reye's syndrome is unknown. An association with chicken pox and influenza B has been clearly shown, but neither virus has been directly implicated. It is possible that in a child in whom the syndrome develops in the course of these illnesses an undetected error in ammonia metabolism may exist. Recent studies of hepatic urea cycle enzymes in Reye's syndrome are consistent with this possibility.

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Gonorrhea from Birth to Adolescence

ONE IN FIVE reported cases of gonorrhea occurs in a person under 20 years old. The number of cases of gonorrhea diagnosed in children correlates as well with the index of suspicion of the physician as it does with the social class of the patient. Gonorrhea in the newborn almost always reflects an infected mother and can be prevented by routine antepartum culture and treatment. Gonorrhea after the first month of life most commonly follows some type of sexual contact, innocent or abusive, in the home. Management of prepubertal gonorrhea must include a search for the source of infection, usually another member of the household.

Gonococcal ophthalmia neonatorum in this country usually represents a failure of silver nitrate prophylaxis, not an absence of prophylaxis. Any conjunctivitis with onset from 12 hours to seven days after birth should prompt a search for the gonococcus. Intravenous administration of aqueous crystalline penicillin G in a dose of 50,000 units per kg of body weight per day for seven days is effective and can save sight. Use of saline irrigations and topical antibiotics in addition to intravenous therapy is recommended. Gonococcal ophthalmia may occasionally be seen in older children.

Postneonatal but prepubertal infection is two to three times more common in girls than in boys. Disease may be manifest as an obvious purulent vaginitis or a minor discharge with labial swelling. Treatment with aqueous procaine penicillin G given in a dose of 100,000 units per kg of body weight intramuscularly and probenecid, 25 mg per kg of body weight given by mouth, is usually effective. Admission to hospital is rarely required. Prepubescent girls may be more difficult to cure than women; follow-up culture is essential. Oropharyngeal and rectal gonorrhea, both more difficult to eradicate than urogenital infection, have been reported in very young children.

Septicemia, arthritis, peritonitis and rarely pelvic inflammatory disease may complicate gonorrhea in children. The efficacy of therapeutic regimens for complicated gonococcal infection in childhood is unproven. The Center for Disease Control recommends 100,000 units of penicillin G per kg of body weight per day for seven days, either aqueous crystalline penicillin given intravenously or procaine penicillin given intramuscularly. Patients over 6 years of age who are allergic to penicillin can be treated with tetracycline, 25 mg per kg of body weight as an initial dose followed by 40 to 60 mg per kg of body weight per day in four doses for seven days.

It is important to recall that eradication of today's relatively resistant gonococci requires high blood levels of antibiotic. Benzathine penicillin (Bicillin®) has no place in the treatment of gonorrhea in any age group. It is important to note that despite recent improvements in culture media, laboratory diagnosis is not always possible. A strongly suggestive clinical picture or smear of pus is sufficient to initiate treatment, although bacterial isolation should always be attempted.

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Valium® in the Treatment of Status Epilepticus in Childhood

THERE ARE NOT MANY true emergencies in medical practice, but status epilepticus is one of those emergencies. It is a continuum of recurring convulsive activity in which there is no recovery between the attacks, or recovery is incomplete. A variety of manifestations are recognized, including prolonged confusional states, petit mal status, prolonged focal or partial seizures, and generalized or grand mal status epilepticus. It is the generalized status epilepticus that is particularly life threatening and may end in death. Mortality rates as high as 23 percent have been recorded.

Status epilepticus, as with other convulsive phenomena, is a symptom of some pathophysiological state rather than itself a specific disease, and a careful, methodical search must be undertaken to determine the cause of that convulsive activity. The many and varied causes of convulsive disorders are well described elsewhere.

When a patient presents in status epilepticus, attention must be given immediately to several actions: providing an efficient and stable airway with adequate oxygen supply, protecting the patient from self injury and administering drugs to control the convulsive activity. Barbiturates of one type or another, paraldehyde and diphenylhydantoin (Dilantin®) have all been used to terminate status epilepticus, but diazepam (Val-

ium®) is generally regarded as the drug of choice.

Undiluted Valium is slowly administered intravenously at 0.3 mg per kg of body weight up to but not exceeding 10 mg over a 2 minute period. If convulsions are not stopped, the same dose of Valium can be repeated in 20 to 30 minutes. Respiratory arrest has been reported during the fourth administration of Valium, and the drug should be administered slowly and in circumstances where resuscitative emergencies can be reliably handled. If the status epilepticus is still not stopped an anesthesiologist should be consulted to anesthetize the patient.

It cannot be overemphasized that meticulous attention must be paid to the oxygen supply, fluid and electrolytes, and the medications and dosages given must be accurately recorded. Once the status epilepticus is controlled, maintenance doses of anticonvulsants must be assured to avoid recurrence of the seizure activity.

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New Perspectives in the Sudden Infant Death Syndrome

A SEEMINGLY HEALTHY INFANT is put to sleep and found dead in bed. Asphyxiation? Aspiration? Child abuse or neglect? None of these. Rather, the infant is the victim of the sudden infant death syndrome (SIDS, crib death, cot death). Typically, a SIDS episode occurs during sleep or following feeding in infants 1 to 6 months old with an associated upper respiratory infection in the winter months. Premature infants and infants from lower socio-economic strata are particularly at risk. With an incidence of 1 in 10,000 births (8,000 deaths yearly in the United States), SIDS is the second most common cause of death in infancy past the first week of life.

Greater occurrence in twins, in family members, in males and in infants with Type B blood, and a reduced incidence in certain geographic areas such as Israel and parts of Scandinavia, suggest a familial or genetic component.

How sudden is the sudden infant death syndrome? Chronicity is suggested from pathological studies which show that in more than half the victims evidence is seen of chronic alveolar hypoventilation and hypoxemia. Autopsy findings include hypertrophied pulmonary arteriolar muscles, an increased ratio of brown to white fat cells, localized right ventricular cardiac hypertrophy, hypoplasia of the carotid bodies and adrenal medulla, and retarded myelinization and astroglial proliferation in medullary centers of the brain stem.

Human investigation focuses on high-risk target infants: (1) siblings of victims, (2) infants with excessive spontaneous apneic episodes during sleep and (3) "near-miss" victims (resuscitated infants accidentally found cyanotic or white without respiration by caretakers).

Pulmonary studies during sleep define several types of spontaneous apnea: *central apnea,* in which air flow at the mouth and nares ceases concomitantly with cessation of diaphragmatic excursion; *obstructive* or *upper airway apnea,* in which air flow at the mouth and nares ceases despite increasing diaphragmatic efforts, and *mixed apnea,* in which central apnea gives way to obstructive apnea. The obstructive and mixed apneas seem particularly hazardous for a SIDS event because of frequent association with cardiac arrhythmias, including runs of bradycardia and ventricular tachycardia. Although the specific location of the obstruction has not been found, functional obstructions are likely to occur at the level of the larynx. A rich and highly specific anatomical nerve supply makes this area particularly vulnerable for reflexive constriction. Spontaneous cardiac arrhythmias without associated apneas also have been observed. Consequently, SIDS victims may represent neonatal precursors of the "prolonged QT interval syndrome" of adults. Finally, several biochemical, neurohumoral and metabolic deficiencies (immaturities) have been observed. Abnormalities in gluconeogenesis (phosphoenolpyruvate carboxykinase deficiency), dopamine synthesis (decarboxylase deficiency) and magnesium metabolism have been especially implicated.

It is to be hoped that in the not too distant future the pathophysiology and causes of SIDS will be elucidated definitively. What can be done now? Repeatedly, it has been shown that, without support, surviving families are particularly vulnerable to marital discord and psychopathological symp-

toms in individual members. Surviving siblings are especially neglected. Community and social recrimination, personal guilt and feelings of inadequacy, concerns about future family planning and ascribing the role of the victim to a surviving sibling are some of the many problems that develop. Efforts directed toward professional and general public education, and psychological support services for families of victims are required. Parental self-help groups and professional counseling should be available.

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Vitamin E Deficiency in Premature Infants: Interaction with Iron

VITAMIN E DEFICIENCY and iron deficiency can both cause anemia in premature infants but by different mechanisms and at different ages. Vitamin E acts to protect the red cell membranes against oxidative breakdown, and a lack of the vitamin results in anemia due to accelerated destruction of red blood cells. A premature infant may become deficient in vitamin E shortly after birth. The basis for this deficiency is the failure to absorb adequate amounts of the vitamin rather than a dietary lack. By 2 to 3 months of age, or at about the time that a premature infant would normally have been born, absorption of the vitamin becomes normal and the anemia is corrected spontaneously, without a change in diet. In contrast to the early development of vitamin E deficiency, iron deficiency anemia is rarely evident before 4 months of age, after tissue iron stores become exhausted. It is due to a lack of sufficient dietary iron to meet the needs of rapid growth, and it results in a decreased net production of hemoglobin, the major iron-containing protein in the body.

Although iron administration is intended to prevent anemia, large doses (8 mg per kg of body weight) given to preterm infants under 3 months of age may actually accentuate the fall in hemoglobin concentration that normally occurs after birth. In such large doses iron is believed to act as a cofactor in the oxidative breakdown of the red cell membrane which at this age is not well protected by the antioxidant action of vitamin E.

There are two ways to reduce the risk of nutritional anemia in premature infants. The first is to use a new water soluble form of vitamin E, alpha-tocopherol polyethylene glycol-1000 succinate (TPGS), during the first three months of life. This form of the vitamin is adequately absorbed even by small premature infants and is already in use in some commercial multivitamin preparations. The second is to avoid maintenance doses of iron above the 2 mg per kg of body weight per day recommended by the Committee on Nutrition of the Academy of Pediatrics. Indeed, it is acceptable to delay administration of supplemental iron entirely until after 2 or 3 months of age since iron stores are rarely depleted before this time.

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Ampicillin Resistant Hemophilus Influenzae *—A New Dilemma*

BEFORE 1973, many reports of therapeutic failures with ampicillin given during treatment of infections due to Hemophilus influenzae, type B were related to inadequate ampicillin administration or persistent foci of occult infections. However, during the latter part of 1973, strains of H. influenzae resistant to ampicillin were involved in a variety of infections including otitis media, acute epiglottitis, meningitis and septicemia. Subsequently, these resistant strains have been shown to produce a constitutive and cell bound beta-lactamase which rapidly destroys many penicillins and cephalosporins, particularly penicillin G and ampicillin. Minimal inhibitory concentrations for ampicillin among these resistant strains are as high as 50 to 200 micrograms (μg) of ampicillin per ml. Since the beta-lactamase produced by these strains of H. influenzae are similar to those produced by Klebsiella, it is specu-

lated that the resistance may be borne on a related R-factor.

Since the continued occurrence of ampicillin resistant organisms appears likely, several therapeutic options have been suggested. In institutions with laboratories able to carry out suggested beta-lactamase assays and sophisticated susceptibility studies, as well as close clinical follow-up of patients, ampicillin may still be the treatment of choice until resistant organisms are proven to be a frequent problem. In institutions with limited laboratory facilities, therapy for serious infections due to suspected hemophilus organisms (that is, meningitis, sepsis, septic arthritis and the like) may be initiated with the combination of ampicillin (200 to 400 mg per kg of body weight per day, intravenously given in six doses) and chloramphenicol (50 to 100 mg per kg per day, intravenously given in four doses) or preferably chloramphenicol alone; therapy can be altered subsequently depending on the results of susceptibility tests. However, it must be cautioned that standard disc susceptibilities frequently are unreliable for H. influenzae. Therefore, proper treatment of these infections will depend primarily upon continuing surveillance of local susceptibility patterns as well as careful monitoring of the individual responses of patients to treatment.

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Imipramine (Tofranil®) in the Treatment of Enuresis

ENURESIS is considered abnormal in any child who consistently wets his bed after five years of age. Because there is no organic basis for the disorder in more than 90 percent of cases, genitourinary workup is held to a minimum. If in a child under 8 years old, there is no history of urinary tract infection, results are negative on urinalysis and concentration is possible to a specific gravity over 1.020, no further workup is undertaken. In children over 8 years intravenous pyelography and cystography are routinely carried out.

Until April 1973, administration of imipramine was not approved for children under 12 years of age. Since then it has been approved for use in children over 6 years. Administration of imipramine is one of the more useful treatments for enuresis in children without organic disease.

The suggested dose schedule is as follows: Children 6 to 12 years old may be started on 25 mg one hour before bedtime. If no improvement is noted, increase the dosage to 50 mg for four more weeks. If no improvement is noted, stop therapy. In patients over 12 years old the dosage may be increased to 75 or even 100 mg at bedtime. When improvement occurs treatment should be continued for three months and then gradually discontinued.

The exact mode of action of imipramine is unknown. Very few mild side effects occur on therapeutic doses. The major danger is accidental ingestion. Severe defects in cardiac conductivity resulting in irreversible heart block have resulted in a high mortality. The recently reported use of propanolol early in the course of accidental poisoning has resulted in a higher salvage rate.

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Anticholinergic Poisoning —New Antidote

THE INCIDENCE of poisoning by commonly used drugs and plants with anticholinergic properties is increasing. In spite of this increase, there is a general lack of knowledge of the specific antidote, physostigmine, for these poisons. Since there is dramatic reversal within minutes of the life-threatening symptoms due to this poisoning, it is essential that all clinicians treating these patients are aware of and skilled in the use of this antidote.

Drugs with anticholinergic properties consist of the tricyclic antidepressants (Elavil®, Triavil®); atropine; scopolamine; belladonna; the antihistamines (Benadryl®, chlorpheneramine); some over-the-counter sleep or calming medications (Sominex®, Compoz®, Cope®—containing methapyrilene); doxepin, and methyprylon (Noludar®).

Common plants with anticholinergic properties

are amanita muscaria, deadly night shade, Jerusalem cherry, jimson weed and lantana.

The clinical picture of toxicity consists of:

Central effects—hyperactivity, delirium hallucinations, disorientations and seizures, coma and death.

Peripheral effects—dilated pupils, vasodilatation (flush) hyperpyrexia, tachycardia, secretion of saliva and sweat, secretions in pharynx and bronchi, urinary retention, serious cardiac arrhythmias.

Administration of physostigmine, an anticholinesterase, dramatically reverses both the central and peripheral effects of these anticholinergic substances, including the cardiac arrhythmias. The initial pediatric dose is 0.5 mg and dosage is slowly increased at five-minute intervals to a maximum dose of 2 mg. The adult dose is 2 mg and it is slowly increased to 4 mg.

Physostigmine is rapidly metabolized and repeated therapeutic doses may be necessary at 30 to 60 minute intervals as symptoms recur.

If toxic effects of physostigmine appear, atropine in a dose half that of physostigmine can be used to reverse these effects.

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Alcohol and Adolescents

THERE HAS BEEN an increase in consumption of alcohol and the consequent problems associated with alcoholic intoxication in children and teenagers. Alcohol-related automobile accidents involving adolescents are increasing. Because of advertising's youth-oriented message, alcohol, beer and wine have been made especially attractive to teenagers. Some of the young drink for social reasons such as peer acceptance, curiosity and experimentation. Others use alcohol as self-medication to relieve tension and anxiety. Self-medication paves the way for drug abuse and alcoholism.

Many families and cultural groups can use alcoholic beverages responsibly. Low-risk groups of drinkers come from families that present a constant example of drinking in moderation without lecturing or preaching. These families have ground rules for using alcohol or not using it, agreed upon by all. Excessive drinking is not acceptable and overindulgence is not looked upon as comical.

Alcohol abuse is at times related to lack of self-esteem and the search for identity. In others, alcohol abuse becomes a way of reducing tension and anxiety when no positive outlet for this energy exists. The ability to deal productively with normal states of anxiety, tension and frustration is based on family patterns of coping that are developed through experience.

Physicians must be alert to family, social and personality problems of those at high risk. Early intervention by those who care for young children and adolescents will be more productive than therapy once alcoholism is established.

MARTIN GERSHMAN, MD

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Cytoxan and Future Sterility

THE USE OF cytotoxic agents in inflammatory diseases was limited in the early period of steroid therapy. As more efficacious and less toxic cytotoxic agents have been developed, they have been used widely in those diseases that cannot be controlled by steroids, such as steroid-resistant and steroid-dependent nephrosis.

Cytoxan® (cyclophosphamide) is the agent most extensively used. Cytoxan is a derivative of nitrogen mustard and has a wide spectrum of biologic activities, including its inhibitory effects on immune phenomena and anti-inflammatory mechanisms. Although this agent depresses gonadal functions in experimental animals, this effect was not generally appreciated in humans until 1972. Then Fairley and co-workers reported that Cytoxan in daily doses of 50 to 100 mg had produced low sperm counts and azoospermia in 31 men. To date, there does not seem to be a permanent depression of ovarian function. Women treated with Cytoxan have delivered normal in-

fants. Cytoxan therapy before puberty has been found to induce permanent sterility in males but not in females. However, in controlled studies, Cytoxan (75 mg per square meter) does not cause sterility if given only for eight weeks. This is adequate in duration and amount to be beneficial in nephrosis. Preliminary observations indicate that a second or third course of Cytoxan therapy for eight weeks appears to be safe. Although this dosage is usually free of side effects, the patient should be instructed that alopecia can occur, but is corrected on cessation of Cytoxan administration. The drug should be given in the morning, followed by a liberal fluid intake in order to minimize the occurrence of hemorrhagic cystitis and fibrosis of the bladder; peripheral leukocytes should be monitored also. Additional long-term controlled trials, with the use of other cytotoxic agents, are in order. Such agents should be used with great caution, however, until more adequate studies have been completed.

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Acetaminophen Poisoning

ACETAMINOPHEN is being used increasingly as a substitute for salicylates. As a result of this utilization, poisonings and deaths from acetaminophen are increasing. It is important for all clinicians and workers at poison centers to be aware of the unique clinical features that this poisoning presents.

Ingestion of toxic amounts of acetaminophen leads to the following course:

Immediate (within a few hours)—anorexia, nausea, vomiting and diaphoresis. Central nervous system depression and coma do not occur.

Delayed (over subsequent 48 hours)—above symptoms continue as liver toxicity becomes clinically evident. There is pain in right hypochondrium with a large and tender liver. Hepatic enzymes, bilirubin and prothrombin levels rise dramatically. Three to five days later there is pronounced hepatic necrosis with jaundice, hypoglycemia, coagulation defects, encephalopathy and death due to hepatic failure.

Acetaminophen is rapidly absorbed from the gastrointestinal tract and metabolized by the liver to an active intermediate metabolite. This metabolite is thought to be the agent responsible for the hepatotoxicity.

Liver damage consists of cellular necrosis particularly in centrilobular areas which results ultimately in hepatic failure. Long-term effects of this damage in survivors have not been determined.

Treatment initially consists of emptying of stomach contents by induction of emesis with ipecac. Plasma acetaminophen level should be obtained. Plasma levels of more than 300 micrograms (μg) per ml of acetaminophen at four hours have been associated with hepatic damage. Once hepatotoxicity has occurred, the only treatment is supportive. Neither forced diuresis nor hemodialysis is effective. Use of steroids has not proved to be beneficial.

For hepatic failure, exchange transfusion and cross-circulations with pigs and baboons has been used with varying success.

Mitchell and his colleagues have reported preliminary success with an agent, cysteamine, which inactivates the toxic metabolite of acetaminophen. This agent, however, is only experimental and not available for clinical use.

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Caffeine (No-Doz®) Poisoning In Childhood

ACUTE CAFFEINE INTOXICATION in pediatric patients may mimic diabetic ketoacidosis in its presentation. Care must be exercised in the clinical diagnosis and treatment of a patient who presents with glycosuria and acetonuria.

Attention was focused on the problem with a 3-year-old child who was recently followed after accidental ingestion of 78 mg per kg of body weight of caffeine (No-Doz®). The child presented with symptoms of coffee ground emesis,

abdominal pain, alternating states of consciousness, copious mucous secretions, palpitations, photophobia, muscle twitching, miosis, clammy distal extremities, pulmonary rales and wheezes and hypoactive deep tendon reflexes. During the first 36 hours after admission to hospital 5 percent sugar by Clinitest® and Labstix® (glucose oxidase), and large amounts of acetone in the urine were noted. Results of additional laboratory studies showed leukocytosis, hypokalemia, mild glycosemia and normal serum insulin.

Von Oettingen outlined the symptoms and signs of acute caffeine poisoning as vomiting, epigastric pain, vertigo, extreme miosis, photophobia, flickering before the eyes, diplopia, amblyopia, visual field restriction, confusion and restlessness, headache, insomnia, tremor, delirium, hallucination, tachycardia, hypotension, cold and clammy skin, labored breathing, and diuresis with possible glycosuria and acetonuria. Boyd and associates reported polydipsia, polyuria, and glycosuria in experimental rats after high dose chronic caffeine administration; however, no mention of acetonuria was made. Bronchopneumonia and pulmonary edema were named as the terminal events.

The toxic dose of caffeine in humans is suggested to be between 2 and 20 mg per kg of body weight, while the lethal dose is felt to be between 140 and 200 mg per kg of body weight. Findings in animal studies indicate that an age related susceptibility factor exists with sensitivity to toxic doses increasing with age. The physiologic effects of acute caffeine overdosage can for the most part be explained; however, glycosuria and acetonuria without glucosemia or acetonemia cannot. Boyd reported the histologic finding of extensive kidney inflammation with the brush border of cells lining the renal proximal convoluted tubules appearing necrotic. Red blood cells filled the loops of Henle and cells of the distal convoluted tubules were swollen to seal off the union. This suggests generalized renal damage with lowering of the threshold perhaps to a number of normal plasma constituents; the mildly elevated blood glucose might be explained on the basis of an adrenal stress factor.

We feel that because of the increased use of caffeine containing insomnics (especially since a palatable form exists) physicians need to be alerted to the effects of caffeine in acute overdosage. One must be alert as to the similar clinical features in patients with diabetic ketoacidosis. Supportive measures as used in other forms of poisoning, such as control of seizures, respiratory arrest, treatment of shock and the use of cardiac depressant drugs may be indicated.

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Meningococcal Prophylaxis

IT HAS LONG BEEN recognized that family members of patients with meningococcal meningitis have an increased risk of contracting the disease. Results of studies of meningococcal carriage rates in contacts have shown an increased likelihood of acquisition of the organism in close family members. The carriage rates drop, however, when compared with schoolroom contacts. For this reason, chemoprophylaxis would seem to be indicated only in close contacts and not for casual acquaintances.

In view of the increasing resistance to the sulfa drugs which the organism has shown since the mid-1960's, these drugs are no longer recommended for chemophophylaxis unless it is known in advance that the organism is from a sensitive strain. Although penicillin can be used to treat an active case, it has not proved useful in clearing the carrier state.

Recently two antibiotics, minocycline and rifampin, have been used with good results in treating carriers. Rifampin is currently being recommended in a dosage of 600 mg twice daily for two days in adults. The pediatric dosage is 10 mg per kg of body weight twice daily for two days in children between the ages of 1 and 12 years with half that dose in infants between the ages of 3 months and 1 year. Minocycline is no longer recommended due to the high incidence of vestibular side effects, including dizziness, nausea and vomiting.

Monovalent vaccines effective against Types A and C meningococci have recently been licensed

for use in epidemic control. These have been used with success in certain military installations as well as in the recent epidemic in Brazil. Since measurable antibodies do not appear until two or three weeks after inoculation, these vaccines would appear to be of little value in the treatment of close contacts of a patient with an active case.

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EDITORIALS

A BICENTENNIAL EDITORIAL

Quality of Life— A New National Purpose?

So FAR there is a curious awkwardness about this bicentennial year. There is remarkably little interest in celebration. Rather as a nation we seem not quite satisfied with what we have accomplished, with where we are or where we are going. We appear to be drifting. Our system does not seem to be working as well as it did, or we thought it did. Many of the social and cultural institutions which have been the fabric for America's greatness seem somehow unable to cope as effectively with today's problems. This surely portends some kind of change. But there is no sense of hopelessness or despair. Rather the contrary. In the midst of all the confusion of unsolved problems a bold new idea seems to be emerging. There is growing talk of something called quality of life, and of making this something available to every person. Quality of life for everyone is a stirring idea and surely one of a grandeur to match the vision of the forefathers who founded this great nation. It could become a new national purpose worthy of our national heritage. But how is quality of life for all even conceivable, what is meant by it and how could it ever be brought about?

It is conceivable first because it is a dream and dreams can be made to come true. But it is also conceivable because of certain facts in the life of present day America. Quality of life first assumes that certain basic material needs have been met. We still have poverty, but the fact is that America has succeeded in meeting the basic material needs of most of its citizens, and many Americans have begun to have a taste of what has been called future abundance. We take this quite for granted and tend to forget that it is actually something quite new in the world. Then there are unmistakable signs that a new humanism has appeared on the American scene, a new and apparently genuine concern with one's fellowman, particularly with those who have been deprived or repressed for one reason or another, whether here or elsewhere in the world, and this can only be significant. There is a new awareness and deep concern with the long-range bioecological viability of the environment—local, national and worldwide. In another dimension a new social, economic and political interdependence among people is becoming clearly evident everywhere modern technology has been applied to any significant degree. Facts such as these foreshadow change and the possibility, perhaps even the inevitability, of a new era when cooperation rather than competition will be the necessary order of the day, and where something like quality of life available to everyone can be a rational goal to be aggressively pursued.

But what is meant by quality of life? Certainly we mean quality of life for people. This obviously must involve such individual things as heredity, cultural background, physical and emotional maturation, and personal fulfillment—while respecting the right of others to the same. It must also include a satisfactory personal lifelong interaction with a complex environment. And the quality of this environment must be adequate for the needs of each individual person and of the species—and for the long-term survival and development of humankind. Thus, the social, economic and political interdependence among human beings will need to be recognized as part and parcel of quality of life. This interdependence will need to become a framework within which cooperation will gradually gain ascendancy over competition as the dominant mode of human interaction. And it seems likely that the commonalities among all people—such as human needs, capacity for communication, response potentials and even a common basis for morality—can become the pathways for this necessary human interaction and cooperation within this framework of human interdependence. The concept will have to be developed and will require study, refinement and action of one sort or another if the idea of quality of life available to every person is ever to take on practical meaning.

America has certainly led the world in being able to meet most of the material needs of its citizens. This goal, worked toward for so long, has only recently been essentially achieved, and the nation now seems to be questioning itself, its pur-

poses and its institutions and their effectiveness. There is a clear sense that something seems to be wrong with America, that we are not quite sure what is wrong or what to do about it. But could it be that rather than having failed or lost our touch, we have simply completed a first phase of our destiny and, at this bicentennial moment in our history, are in the process of disassembling much that is no longer needed or useful, and are actually in a transitional phase between a dynamic past and a new dynamic future? And might it be that trying to make quality of life available for all people is to be our pacesetting goal for the future? It is an idea that seems just as visionary and just as worthy of America today and for the era that lies ahead of us now as was the vision of the founding fathers for the era that lay ahead of them two hundred years ago. And it will take leadership and energy in the same sort of grand dimensions to accomplish it. But it could become the national purpose for which we seem to be groping.

One wonders what might be the role of medicine. Obviously quality of life is something physicians seek for their patients. But beyond this, what other profession is any closer to the concept and meaning of quality of life—which is so intimately linked to the physical, mental and, yes, the social well-being of every person? It would seem that medicine could and perhaps should prepare itself for a role of leadership, a role of physician to a society groping for a new purpose in what is already becoming a new era for mankind in world history.

—MSMW

Congenital Dislocation of the Hip—Then and Now

As Elmer Specht notes in his Medical Progress article elsewhere in this issue, congenital dislocation of the hip is an affliction as old as man himself. It was recognized in ancient Egypt, Greece and Rome by physicians as a specific skeletal abnormality but one which was usually painless and of relatively low morbidity.

Before 1880, when Buckminster Brown, Professor of Orthopaedic Surgery at Harvard, attempted to reduce a congenital dislocated hip, the condition was considered incurable. Infant girls are affected at least eight times more frequently than infant boys and in one child out of 1,000 born in the United States, one or both hips are dislocated. Despite much theory, argument and conjecture, the cause remains unknown.

During the past century, much has been written about the pathological anatomy, the physical signs, the incidence in certain ethnic groups, the nature of inheritance and the type of treatment indicated in specific age groups. Between 1880 and 1950, physicians emphasized manipulative reduction after the techniques of Lorenz, Davis, and Denucé, but they failed to understand the delicate nature of epiphyseal cartilage and its circulation so that many hips were reduced but with sufficient force to permanently impair further normal development of the joint.

The last quarter century has seen vast changes for the better in the treatment of this common congenital abnormality. Careful orthopaedic examination of newborns has taught physicians that absence of the normal neonatal flexion contracture of the hip and contracture of the adductor tendons in the groin strongly suggest the diagnosis which can be confirmed by appropriate radiographs, even in a neonate.

Infants under 1 year of age can be treated with a simple pillow-splint to hold the legs abducted at the hips. Use of this type splint, in addition to exercises supervised by the mother, will result in a very high percentage of excellent results. A child with a shallow acetabulum, a so-called dysplasia, will also respond quickly to such simple therapy. Closed gentle manipulative reduction under general anesthesia combined at times with adductor and iliopsoas tenotomy will yield excellent hips in 80 percent of children under the age of 3.

Because of the small size of anatomic structures involved and because of the occasional poor differentiation of tissues about the hip, open surgical reduction is not advised in a patient under the age of 3. After age 3, open reduction is indicated because of the contracture of tissues about the hip, because of constrictions in joint capsule and because of the development of intraarticular soft parts which prevent accurate reduction by closed methods. The emphasis again is upon gentle replacement of the femoral head into acetabulum

to prevent circulatory impairment or epiphyseal injury or both. Following open reduction, a derotation osteotomy of the femur may be required to treat severe anteversion of the femoral head and neck.

The failure of adequate acetabular development in the first decade of life has led to the significant contributions of Pemberton[1] and Salter.[2] The procedure of Pemberton effectively decreases acetabular volume by means of a pericapsular osteotomy of the ilium, whereas the Salter innominate bone osteotomy shifts the relationship of the acetabulum to femoral head but does not change acetabular volume. Both procedures provide good, long-term results but they must be carried out precisely in accord with the indications meticulously described by the authors.

The importance of careful observation of all children to skeletal maturity is stressed. Occasionally the acetabulum fails to participate normally in the final adolescent growth spurt. The femoral head grows unevenly due to lack of acetabular cover, and if this disparity is undetected and untreated an instability of the hip occurs, manifested by intermittent limping and pain with activity—which can lead to crippling degenerative arthritis in middle life. A carefully carried out acetabular shelf procedure provides appropriate treatment for this problem and returns the child to an active life.

The significant contribution of Ashley and his associates[3] to reduction of the dislocated hip in older children again stresses gentle reduction by means of removing a segment of the upper femur, thus permitting the head to reduce into the acetabulum without force.

Fortunately, we are now in a phase in the treatment of congenital dislocation of the hip when—because of better understanding of the patterns of inheritance—reasonable genetic counseling can be given to parents, particularly if one or both were born with the disorder. Use of brute strength in the reduction of the dislocation has fortunately disappeared, to be replaced by methods of treatment based on the concept of gentle handling of delicate growing bone.

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A BICENTENNIAL EDITORIAL

The Third Hundred Years — Regulation Will Be the Rule; But How?

REGULATION IS ALREADY with us and of necessity it will be the rule henceforth if we are to thrive as a nation. The reason for this is that technology, industry and the social, economic and political institutions of America have become irreversibly and progressively interdependent. Such interdependence requires some order or governance if the parts and the whole are to run smoothly and efficiently. It therefore is not a question of whether there will be regulation, but rather of how the needed regulation will be accomplished, and more importantly whether or not an increasingly interdependent society can govern itself or will it have to be governed?

The health care industry in all its facets—education, research, the training of personnel, facilities, supplies and productivity in the way of services—seems to be the crucible in which these questions are being first tested. Furthermore a pattern may be set here which will then be applied elsewhere for governance and regulation in our interdependent society. One may speculate on why it is that health care could turn out to be the proving ground. Perhaps it is only because from a federal standpoint a healthy nation is a strong nation. But for whatever reason, health and health care have become a major concern of government, particularly of the federal bureaucracy, and more recently of the Congress as well. And for whatever reason, the question of how to govern a complex interdependent social system which intimately affects the lives and well-being of many, if not all citizens is obviously coming to a head in the field of health.

There is no real precedent in our democratic system for regulating such a complicated business as health care. It has done no good to consider it a "non-system." In keeping with such precedent as there is, the federal government has

evolved a more or less coordinated (within government) effort to bring about the regulation of health care and the health care industry by use of the traditional means of the federal bureaucracy. It has done this by developing its own premises, its own plans, its own laws and its own regulations which also have the force of law. By these means the government has sought to regulate health care supplies, facilities, research, education and training of personnel, and the rendering of services to patients and the public—in short the whole system. But so far this quite massive effort has not produced anything like what was expected in the way of the desired results. Over the past decade there have been many failures of regulations and programs, friction and inefficiencies within the system have increased, costs have risen beyond all expectations, and there is all too little evidence that either health or health care is very much better.

Some of the reasons why this bureaucratic approach does not and really cannot work are beginning to become evident, although they are by no means yet generally recognized. For one thing simplistic premises, and rules derived from them, probably just do not apply in complex systems that are inherently dynamic and constantly changing even while they are being studied or regulated. For example, the premise that if more money were pumped into health care the health of the public would be proportionately improved was found to be incorrect, the reason being that neither the complexity of the system nor what would happen to the money was either understood or taken into account. For another it is probably impractical, if not impossible, to govern any such complex and constantly changing system by rules established by persons outside of that system and not a part of it. The rules too often turn out to be unrealistic and even counterproductive. And third, if any governance or regulation of such a system is ever to work smoothly and efficiently, it should have the consent and also the support of those who are to be governed or regulated. And this has certainly not been sought or achieved by government in the field of health care.

There is no escaping the problem of regulation whether in health care or elsewhere in our interdependent society. Perhaps a basic question should be asked once more. Can a society or a social system, however complex and interdependent, ever govern itself or will it always have to be ruled or governed? Or is there a possibility of some approach which would preserve the right of self-government, within a framework of what must be done to assure the stability of the whole of our complex interdependent social system? These are fundamental questions, pertinent to our American view of the role of government, with which we as a nation will have to come to grips and which we will have to solve very soon. And the outcome will determine the governance of America for the third hundred years of its history and perhaps longer.

It would seem timely and even essential to try to get back to the principle of governance with the consent and support of the governed. Perhaps what is needed are mechanisms for a degree of self-government in fields such as health care, mechanisms that could do whatever needed to be done in the way of regulation, but do it in such fashion that it would have the consent and support of the governed, and also be within a framework of what must be done for the welfare and stability of the whole interdependent social system. Perhaps health care is a field where some such approach might be tried, at least as an experiment. In any case there is need for some new and far more sensitive and sophisticated system of providing for necessary regulation. It is far from satisfactory, and it may not even be possible, to force a complex and ever changing system such as health care into a relatively fixed mold that can be managed by the traditional bureaucratic methods which are all that are now available to the government.

A genuine new approach is needed. This is a fundamental challenge for our next hundred years as a nation. Perhaps a start can be made in health care where the patterns for the future seem to be being set now. There is a magnificent opportunity for leadership for medicine, perhaps the most important opportunity so far in the history of this great nation. As physicians we should initiate whatever action is necessary to make the health care industry, in all its aspects, a model capable of self-regulation within the framework of the needs and capabilities of an increasingly complicated and ever more interdependent human society. But can or will we? This is an important question. Our leadership seems almost totally absorbed with more immediate, though perhaps no less pressing, problems.

—MSMW

Pulmonary Alveolar Proteinosis

WE HAVE TREATED 14 patients with pulmonary alveolar proteinosis by lung lavage, some more than once. In each case, the initial treatment was given because the patient was progressively deteriorating and unable to work, or, in the case of two small children, cachetic and near death. In each case, lung lavage reversed the clinical course.

In 1968, I coauthored a paper on treatment of a patient with pulmonary alveolar proteinosis, whom I had seen in 1966 while on the staff at Stanford.[1] In this paper, we reported the physiological and radiological changes of that patient after left and right lung lavage. Chest roentgenograms, gas exchange and blood gas measurements before and after each lung lavage documented the improvement. The observations reported in this paper reflect the type of improvement that we have noted in the 13 other patients. By the evening of the lavage of the left lung (we always do the left first), findings on physical examination usually show greater expansion of that lung when contrasted with the expansion of the right lung. The patient may comment that the left side feels lighter. Findings on an x-ray film of the chest done on the afternoon or evening following left lung lavage are also very interesting. While the right lung retains its infiltrates, the left lung is in large part cleared of infiltrates. By the next day, the patients comment on their new-found breath as they walk around the ward or climb the hospital stairs. We know of few instances in medicine where the effects of therapy are so immediate and so striking, and have viewed lung lavage as being as specific for pulmonary alveolar proteinosis as penicillin is for pneumococcal pneumonia.

Since our observations differ so notably from those described in the Lewiston-Robin symposium in this issue of the JOURNAL, one might wonder if lung lavage is done differently by different groups. The whole lung lavage technique, as we do it, differs from the original description of Ramirez and co-workers[2] in several respects. A single lung lavage procedure consists of 12 to 15 lavages of the degassed lung of approximately 1 to 1½ liters normal saline solution, each taking approximately five minutes to carry out. Thus, we use approximately 20 liters of saline solution rather than the much smaller volume (approximately three liters) used by Ramirez and co-workers.[2] We do not find that addition of heparin or acetylcysteine to the saline solution makes the lavage more effective. We percuss during the lavage with a mechanical percussor. We take great pains to regenerate normal surface forces after the lavage before removing the Carlen's tube. The basis of each of these modifications and their details are described in Reference 3. Two of our former fellows have recently treated patients with pulmonary alveolar proteinosis at different hospitals using the procedure that we have described, and have obtained the gratifying results that have been our experience. I suspect that less successful results are due to lack of attention to detail which has been our concern.

The symposium suggests that lung lavage might result in lung damage. There is no question that lung lavage washes out surfactant from the lungs. We can see evidence for this by examining the size of the bubbles in the foam of the first lavage effluent as compared with subsequent ones. The first lavage effluent contains many uniformly small bubbles (approximately 0.1 mm) on the surface. Later effluents have larger bubbles on the surface with only a few small bubbles. The size of the surface bubbles is not related to the quantity of sediment. The reduction in numbers of stabile small bubbles must be secondary to the reduction in the quantity of surfactant in later lavages.

In recognition of this problem, we have always been concerned with the possibility that removal of the surfactant by the lavage procedure would result in a lung with reduced compliance when reinflated with air. Because of widely different compliances between the lavaged and gas exchange lung, the lung with lower compliance or greater recoil force (lavaged lung) would tend to become atelectatic while the lung with the higher compliance or lower recoil force (gas exchange lung) would develop compensatory overexpansion. Therefore, with the Carlen's tube still in place, we suction saline and then foam between ventilations of the lavaged lung. We measure the pressure-volume characteristics frequently. We continue this until the pressure-volume characteristics of the lavaged lung are the same as those of the gas exchange lung. This is usually the same compliance as that measured before the lavage procedure. We do not remove the Carlen's tube until the compliances of both lungs are the same. This takes approximately one hour from the time the lavage procedure is discontinued. This is evidence

that the normal surface forces can be rapidly regenerated after surfactant is washed off the surface lining of the lung. Several hours following lavage of the left lung, there is evidence, from the movement of each side of the chest, that the left lung has a higher compliance than the right lung. Gas exchange is also better by this time, as evidenced by a reduction in the alveolar-arterial oxygen difference. Thus, lung lavage as we do it does not appear to damage the lungs of patients with pulmonary alveolar proteinosis. Parenthetically, in a total of 40 lung lavages done on our 14 patients (in each patient two lavages were carried out, one for each lung; in some patients repeat lavages were required), a low-grade fever was observed only once and this lasted for only 24 hours. We do not give our patients antibiotics before or after the procedure.

Our longest follow-up is that of a 31-year-old woman in whom we carried out lavage at age 23 (1967) because of severe exertional dyspnea. The resting arterial oxygen pressure in this patient was 42 mm of mercury. After lung lavage, she was notably improved and arterial blood gases were normal; in fact, she felt normal and soon returned to work. One year later the patient returned to see us because of increasing symptoms. She asked to have another lavage procedure done. Consequently, we repeated it with the same results as were obtained during the preceding year. This happened two more times, the last being in 1971. Since that time, the patient has been in complete remission and able to work regularly. Four other patients had more than one lung lavage in our series, all at their request. Apparently, the disease process eventually smolders out. The objective of lung lavage should be to prevent the progressive deterioration of the patient's condition which may lead to a hypoxic death and to leave the patient asymptomatic after the disease process becomes quiescent. At this time we have no evidence that the lavaged patients will have a shortened life expectancy. This is important because this disease generally afflicts young people who are interested in obtaining life insurance policies. Life insurance companies have hesitated to insure them.

In the symposium, Dr. Robin suggests that pulmonary alveolar proteinosis is a disease which is now disappearing. Because pulmonary alveolar proteinosis is rare, any single physician might have a limited ability to evaluate its incidence. In contrast to Dr. Robin's observations, we are of the opinion that pulmonary alveolar proteinosis may be increasing in incidence. We have seen five new cases of pulmonary alveolar proteinosis in the past year. This represents a higher yearly new case rate than we have seen in the past. I do not think that Dr. Robin's or my experiences can be used to determine if the incidence of this disease is changing. Since it was suggested that the occurrence of the disease might be related to changes in the environment,[4] it would be appropriate for the Environmental Protection Agency to make this a reportable disease, thus establishing a registry for incidence and geographical location.

From the point of view of the patient's management, I would question the wisdom of the use of the term "secondary" pulmonary alveolar proteinosis to describe disorders of known cause just because there is some anatomical similarity to pulmonary alveolar proteinosis (Table 2 of the symposium). While these disorders might have alveoli filled with amorphous granular material, as seen in pulmonary alveolar proteinosis, they are usually associated with chronic inflammatory changes including fibrosis. To label these disorders as pulmonary alveolar proteinosis distorts their true cause and may be misleading to the understanding of the natural history and cause of pulmonary alveolar proteinosis. The hallmark of true pulmonary alveolar proteinosis is the presence of amorphous granular material in what otherwise appears to be normal alveoli, and minimal lung destruction, fibrosis and inflammation. It is this characteristic which renders it particularly susceptible to treatment by lung lavage techniques.

Finally, I would like to add to the bibliography on this subject the 1965 article by Larson and Gordinier[5] since it represents the largest review of reported cases. In spite of the fact that it was published ten years ago, it is extremely comprehensive and beautifully summarizes much of what we know about the disease today.

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CASE REPORTS

Refer to: Sung JP: Treatment of disseminated coccidioidomycosis with miconazole. West J Med 124:61-64, Jan 1976

Treatment of Disseminated Coccidioidomycosis with Miconazole

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SINCE 1956, amphotericin B has been established as an effective drug for the treatment of various systemic mycotic infections. Unfortunately, its effectiveness has been hampered by its untoward side effects or toxicity.[1,2] Since the condition of the patient discussed in this report was deteriorating from the disease and side effects of amphotericin B, treatment was begun with miconazole, a synthetic 1-phenethyl-imidazole derivative.[3] The drug appears to be safe, with broad-spectrum antifungal activity.[4,5]

Report of a Case

A 50-year-old black man came to the San Joaquin Valley from Louisiana in 1970. He worked in a cotton field until March of 1973 when he started work in a grain mill. He was in good health until five months later when he began to tire easily. In October 1973, cough, night sweats, anorexia, fatigue, weight loss and occasional chest pain developed. Despite three months of treatment with antibiotics and lancing of the abscesses by his private physician, his condition progressively deteriorated, the patient lost more than 40 pounds and new abscesses continued to develop.

The patient was first admitted to the Fresno Veterans Administration Hospital on January 21, 1974. The abnormal physical findings were confined to the skin and subcutaneous tissues. Several tender nodules of various sizes, the largest measuring 6 cm in diameter, were found on the right shoulder, left flank, upper arms, right hip, upper thighs and left upper lip. There were also several healed scars from previous lanced abscesses. The temperature taken orally was 39.4°C (103°F), and pulse was 100 per minute. The lungs were clear, except for a few rhonchi at the bases. The remainder of the physical findings were normal.

Findings on x-ray studies of the chest, right shoulder and hips included no abnormalities. The hemoglobin was 11.2 grams per 100 ml, hematocrit 37 percent, leukocyte count 19,800, with 93 percent neutrophils. Blood urea nitrogen was 7 mg per 100 ml, serum creatinine 1.0 mg per 100 ml and liver profile normal. Results of coccidioidin skin tests were negative at 1:100 and 1:10 dilutions on repeated examinations. Findings on a coccidioidal spherulin skin test were also negative. Direct smear from the abscesses yielded spherules of Coccidioides and culture grew typical colonies of Coccidioides immitis. On biopsy of the fungating upper lip lesion, a coccidioidal granuloma was noted. The complement fixation titer was 4 plus at a dilution of 1:125.

Despite therapy with amphotericin B given intravenously, abscesses continued to develop that required frequent incision and drainage. Temperature ranged from 38.3°C (101°F) to 40.6°C (105°F) for 80 days. Leukocytosis with a left shift persisted. After four weeks of amphotericin B therapy, the blood urea nitrogen rose from 7 to 55 mg, and the serum creatinine from 1.0 to 2.8 mg. Both values returned to normal when the drug was discontinued and the dosage schedule modified. During amphotericin B treatment, the patient experienced headache, nausea, vomiting, anorexia, chills and fever. A total of 2.25 grams of amphotericin B was given during a 90-day period. During the last two weeks of therapy, the patient's general condition improved with only one small nodular lesion remaining on the right shoulder. He was discharged from the hospital on April 23, 1974, to be followed in the Outpatient Clinic.

The patient was readmitted to the hospital on August 26, 1974, with severe pain in the right shoulder and a recurrent tender coccidioidal ab-

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Figure 1.—Destructive lesions of scapula and acromion, and greater tuberosity of humerus of right shoulder despite administration of amphotericin.

scess on the right side of the neck. One month before admission, the patient stated he had had periodic chills and fever. On physical examination, diffuse tender swelling over the right shoulder and a fluctuant mass on the right side of the neck were noted. The temperature taken orally was 38.5°C (101.3°F), lungs were clear and findings on an x-ray film of the chest were normal. However, on an x-ray study of the right shoulder, bone destruction of the right scapula and right acromion and greater tuberosity of the right humerus were noted (Figure 1). Erythrocyte sedimentation rate was 38; leukocyte count 17,800 with shift to the left; hemoglobin 12.6 mg per 100 ml, and levels of serum bilirubin, alkaline phosphatase, serum glutamic oxalic transaminase and lactic dehydrogenase were

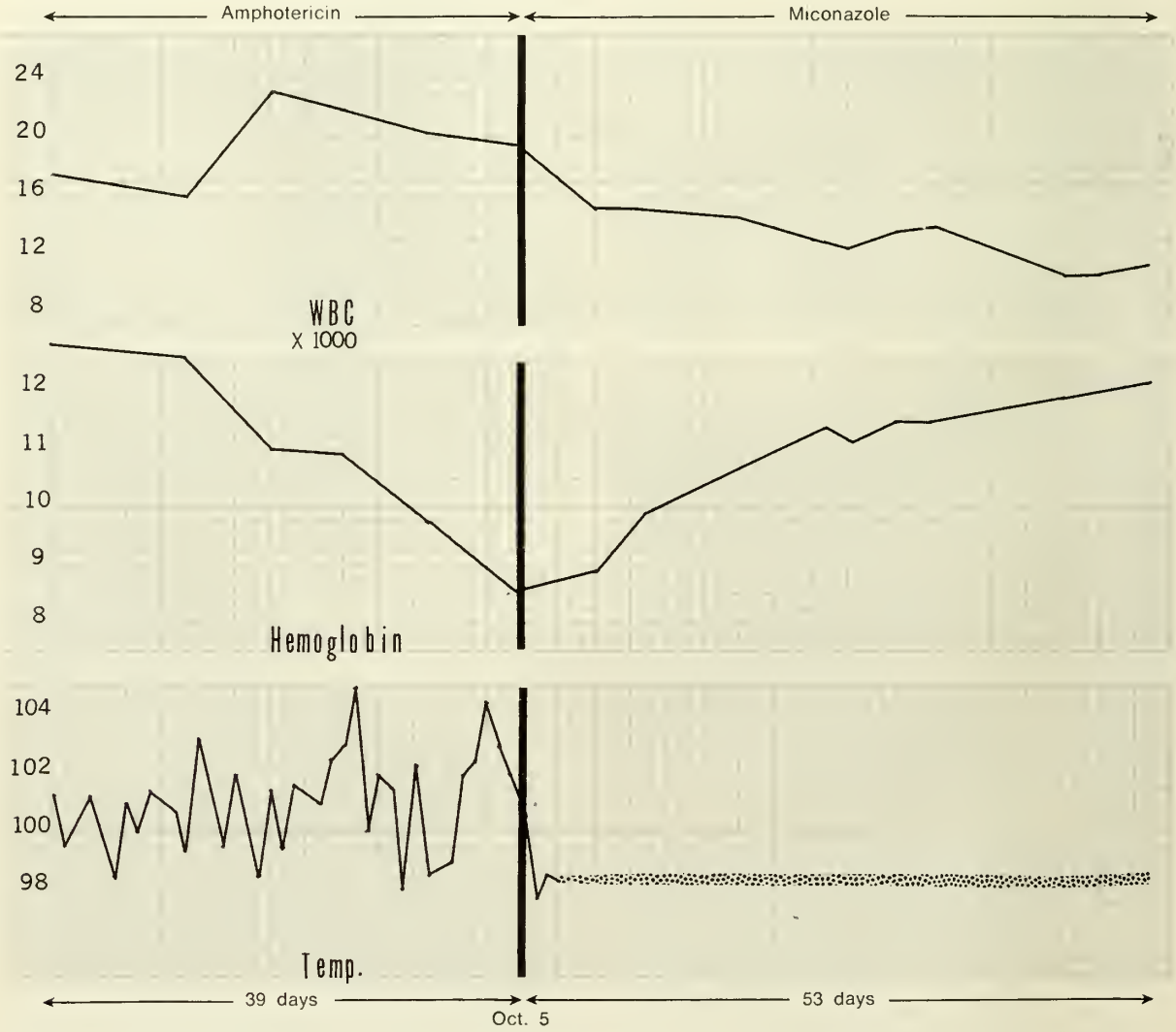

Figure 2.—Comparative clinical course during amphotericin and miconazole therapy. (WBC indicates leukocyte count.)

Figure 3.—Healing of bony lesions of right shoulder after six weeks of miconazole administration.

within normal limits. Coccidioidal complement fixation titer was 4 plus at a dilution of 1:250.

Another course of amphotericin B therapy was started at 50 mg per day, but the patient's general condition deteriorated and several new coccidioidal abscesses developed that required multiple incisions and drainage. A painful new lesion appeared on the left shoulder and grew to 16 by 17 cm within a few days. The temperature spiked to 40.6°C (105°F) and leukocyte count was 24,000 (Figure 2). Hemoglobin decreased from 12.6 grams to 8 grams after four weeks of therapy. The patient became unable to leave his bed and severe weakness, weight loss, nausea, anorexia, emesis and headache were present.

On October 5, 1974, administration of amphotericin B was discontinued after a dose of 1.75 grams for this course and a cumulative dose of 4 grams had been given. After obtaining informed consent from the patient, 200 mg of miconazole,* diluted in 150 ml normal saline, was infused over a 30-minute period every eight hours by central venous catheter, since all peripheral veins had been thrombosed during amphotericin treatment. The patient's temperature returned to normal limits the day miconazole therapy was started and remained normal throughout the remainder of the hospital stay (Figure 2). The leukocyte count slowly returned to normal and the hemoglobin gradually increased without supplementary iron being given (Figure 2). Without incision and drainage, the large mass on the left shoulder subsided completely within 3½ weeks after treatment with miconazole was begun.

*Drug supplied by Janssen R&D, Inc., 501 George Street, New Brunswick, New Jersey.

The dose of miconazole was gradually increased to 400 mg every eight hours, then to 600 mg every eight hours without any notable side effects. When the dosage was increased to 800 mg every eight hours, the patient began to experience dryness of the eyes and mild pain in both knee joints. These symptoms completely disappeared after the dosage was reduced to 600 mg every eight hours. No more nausea, vomiting, anorexia or headache occurred—all of which were commonly encountered during the amphotericin B therapy. The patient gained both weight and strength. During miconazole therapy, skin and subcutaneous lesions healed and no new lesions appeared. After six weeks of miconazole therapy, it was noted on an x-ray study that the osteomyelitis of the right shoulder had healed and no new lesions appeared (Figure 3). The complement fixation titer remained 4 plus at 1:250 dilution. There were no untoward effects from the miconazole after a total of 68.4 grams over 59 days had been given.

Discussion

The mortality and morbidity from disseminated coccidioidomycosis in the black race with negative findings on skin tests are very high. Up to this time, except for amphotericin B, no other effective systemic antifungal agents have been available.

Miconazole nitrate, a substituted 1-phenethylimidazole with a molecular weight of 479.16, is synthetized by Janssen Pharmaceutica in Belgium and is a broad-spectrum antimycotic agent with antibacterial activity.[3] It inhibits the growth not only of most pathogenic fungi but also Gram-positive bacteria.[5] It has been available in Europe since 1971 and in the United States since April 1974, for topical use only. An intravenous preparation is available for investigational use only. Trials in Europe show the intravenous solution to be safe and effective in the treatment of systemic mycoses.[4-7] Since 1973, several cases of systemic candidiasis were treated with intravenous miconazole by Scheef and co-workers and Daneels and co-workers with good results.[6,7] One case of Candida albicans septicemia in a 51-year-old patient after renal transplantation was successfully treated with intravenously administered miconazole by Zazgornik and associates.[8] Hoeprich and Goldstein[9] recently reported their use of miconazole in a patient with coccidioidal meningitis who died of an unrelated complication

after 22 days of treatment. No side effects or systemic toxicity were observed from intravenous infusion of 1.2 grams per day for 30 days by European investigators.

The highest dosage used intravenously in Europe was 1.2 grams per day in divided doses. Due to the severe disseminated disease in this black patient, the intravenous dose was carried from 200 mg to 800 mg every eight hours. The dosage of 600 mg every eight hours was well tolerated. There were no immediate local or systemic side effects and no hematologic or biochemical abnormalities after a total of 68.4 grams of miconazole was given in 59 days. The serum concentration of the drug, after 400 mg intravenous miconazole, was 0.42 micrograms per ml after 2½ hours, and 0.22 micrograms per ml after 7½ hours, respectively. However, no attempt was made to use the serum level of miconazole as a guide for daily dosage administration. In our mycology laboratory, the minimal fungicidal concentration of miconazole *in vitro* was 0.218 micrograms per ml.

Despite its early investigational status and unknown potential for delayed side effects, the dramatic effectiveness of miconazole in a patient with coccidioidal osteomyelitis and disseminated abscesses and granulomata makes it worthy of further clinical trial.

Summary

A fulminating case of disseminated coccidioidomycosis in a black man was refractory to amphotericin B therapy, but successfully treated with miconazole. No immediate side effect or toxicity was observed with intravenous doses of up to 1.8 grams per day. The safety and effectiveness of this drug are worthy of further clinical study.

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Refer to: Garfinkle SE, Chiu GW, Cohen SE, et al: Spontaneous perforation of the neurogenic urinary bladder. West J Med 124:64-66, Jan 1976

Spontaneous Perforation of the Neurogenic Urinary Bladder

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ALTHOUGH SPONTANEOUS PERFORATION of the bladder has been reported in the literature,[1-4] little attention has been focused on its occurrence in patients with neurogenic bladder disturbances. Two cases of peritonitis due to spontaneous intraperitoneal perforation of the urinary bladder in neurologically handicapped patients were recently seen on the general surgical service at the University of California, Davis, Sacramento Medical Center.

Reports of Cases

CASE 1. A 21-year-old man sustained a fracture dislocation of the fourth and fifth cervical vertebrae in an automobile accident. The injury resulted in a spastic paralysis below the level of the sixth cervical vertebra. While the patient was in hospital, urinary drainage was instituted with an indwelling urethral catheter. Two years later the patient was readmitted for treatment of sacral decubiti and multiple bladder calculi. Cystogram disclosed a "Christmas tree" appearance of the bladder and bilateral ureteral reflux. Intravenous pyelogram showed small radiopaque calculi in the right renal pelvis. Results of cystometric examination were consistent with a spastic neurogenic bladder. A cystolithalopaxy was done. Postoperatively, the indwelling catheter was removed and

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the patient discharged with condom catheter drainage.

Eight months later the patient was readmitted with pneumonia. Following this admission, nausea, vomiting and abdominal distention occurred, and findings on roentgenograms of the abdomen were compatible with an ileus. Surgical consultation was obtained, abdominal paracentesis carried out and grossly purulent material was aspirated. Celiotomy was done and a perforation of a bladder wall abscess was found. The necrotic portion of the bladder was excised, the defect closed and a suprapubic cystostomy established. The postoperative course was complicated by an episode of septic shock and disseminated intravascular coagulation. Intermittent episodes of sepsis finally resolved following ureteroileostomy.

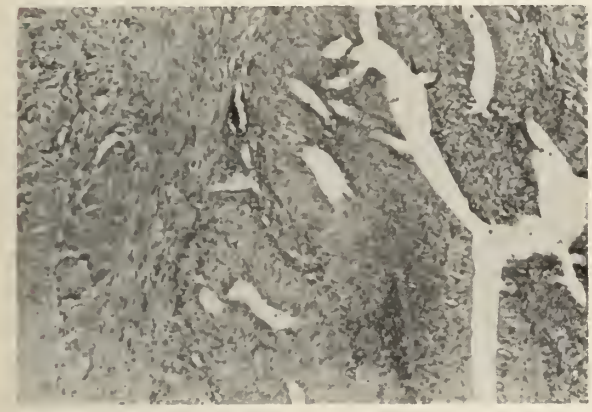

Figure 1.—Photomicrograph of bladder in area of perforation in Case 2 showing pronounced inflammatory changes.

Figure 2.—Cystogram (Case 2) showing extravasation of contrast from bladder into peritoneal cavity.

CASE 2. A 74-year-old woman entered the emergency department with a 24-hour history of abdominal pain and progressive obtundation. One episode of vomiting had occurred before admission. Bowel movements had been regular. The remainder of the gastrointestinal history was negative. Five years previously, cerebral thrombosis resulted in a right hemiparesis, chronic organic brain syndrome and urinary incontinence. Catheter drainage of the urinary bladder was instituted, but the catheter was repetitively removed by the patient.

On admission the patient was cachectic and obtunded with a blood pressure of 80/0 mm of mercury. A supraventricular tachycardia of 170 per minute and a temperature of 38.9°C (102°F) rectally were present. Positive physical findings included (1) flexion contractures of the hips and knees, (2) a protodiastolic gallop rhythm and (3) abdominal tenderness in the right lower quadrant with voluntary muscle guarding in both lower abdominal quadrants. Intestinal sounds were normal. Results of rectal and pelvic examinations were within normal limits. A hemoglobin determination was 14.9 grams per 100 ml, and the leukocyte count was 3,400 per cu mm with 52 percent nonsegmented neutrophils, 3 percent segmented neutrophils and toxic granulations of the neutrophils. A nonspecific intestinal gas pattern with no free intraperitoneal air was present on the abdominal roentgenogram. Electrocardiographically, a sinus tachycardia and left bundle branch block were noted to be present. Resuscitative measures were instituted with the intravenous administration of fluids, antibiotics (penicillin and garramycin) and hydrocortisone. After ten hours of treatment, pulse rate diminished to 128 per minute, blood pressure increased to 120/90 mm of mercury and central venous pressure rose from 0 to 11 cm of water. Abdominal paracentesis yielded grossly purulent material. At operation a perforated, necrotic diverticulum of the bladder wall was excised (Figure 1), the defect closed and a suprapubic cystostomy established. The patient improved and was discharged on the 21st postoperative day.

One month later the patient was readmitted to the hospital, having removed the suprapubic tube 48 hours earlier. On physical examination, signs of an acute condition within the abdomen were present. Cystography (Figure 2) showed intraperitoneal extravasation of the dye from the urinary bladder. On operation, a new perforation in

the area of the previous bladder closure without disruption of the suture line was noted. The new perforation was closed and suprapubic cystostomy reestablished. The postoperative course was uncomplicated.

Discussion

Previous reports of spontaneous perforation of the urinary bladder have emphasized chronic infection, bladder outlet obstruction[1] and indwelling urethral catheters[5] as etiologic factors. Cystography has been recommended as a diagnostic aid.[3] The mortality rate associated with spontaneous perforation has ranged from 47 to 57 percent.[1,3] The difficulty in establishing diagnosis early, however, has not been widely appreciated, nor has the neurogenic bladder itself been emphasized as an underlying factor in spontaneous perforation.

The patients in cases presented are representative of a large number of neurologically handicapped persons living today. Because of improved rehabilitation techniques, patients with neurologic deficits are living longer and presenting a previously undocumented spectrum of disease peculiar to paralyzed patients. The lack of conventional response to pain following spinal cord injury or cerebrovascular thrombosis decreases the diagnostic accuracy of a history and physical examination in acute abdominal emergencies, and the subsequent delay in diagnosis increases the morbidity and mortality rates. Infections and obstructive urinary tract complications are well documented in the long term management of patients with neurogenic bladder.[7,8] Spontaneous perforation may also occur. In such cases, patients may present with unexplained fever or ileus. We have found that the use of diagnostic abdominal paracentesis has made earlier diagnosis of peritonitis possible in neurologically handicapped patients. Abdominal paracentesis as described by Root[6] can also be used when abdominal distention is present. In such instances the paracentesis catheter is placed intraabdominally under direct vision through a small midline abdominal incision. Fluid obtained is cultured and analyzed for red and white blood cell determinations, amylase and bile. If less than 30 ml is aspirated, lavage of the peritoneal cavity with 20 ml per kg of body weight of Ringer's lactate solution (maximum of 1,000 ml) is carried out, followed by aspiration of the infused fluid. We are currently evaluating criteria for the diagnosis of peritonitis when the fluid aspirated is not grossly purulent.

Operative treatment of a perforated neurogenic bladder consists of excision of the necrotic bladder with primary closure of the defect and suprapubic drainage. Long-term measures to prevent perforation of such bladders include treatment of established urinary tract infections and prevention of urinary retention by catheter drainage, transurethral resection of the bladder neck or supravesical diversion.

Summary

Two cases of spontaneous perforation of a neurogenic bladder are presented. The problem of early diagnosis in neurologically handicapped patients is discussed, abdominal paracentesis is emphasized as a diagnostic aid and the emergency operative treatment of perforated bladder is outlined. This diagnosis should be considered in the evaluation of an acute condition within the abdomen, a fever of unknown origin or an unexplained ileus in patients with neurologic deficits.

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Refer to: The founding of a medical service bureau in King County, Washington—1933 (Medicine in Perspective). West J Med 124:67-69, Jan 1976

The Founding of a Medical Service Bureau in King County, Washington—1933

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The events leading to the establishment of the King County Medical Service Corporation, now King County Medical-Blue Shield, were varied and complex. Under pressure, the King County Medical Society redefined its code of ethics, expanded its view of acceptable practice and gave birth to a major provider of prepaid health care services.

THE KING COUNTY MEDICAL SERVICE BUREAU, largest of 20 such organizations collectively known as the Washington Physicians Service, is a major provider of prepaid health care coverage and a Part B Medicare "carrier" in Washington State. Some 1,800 physicians serving more than 300,000 people provide a stark contrast to the neonatal group formed first nearly six decades ago. In May 1917 the King County Medical Society, prodded by the passage of the Medical Aid amendment to the Washington State Workmen's Compensation Law, founded what the author believes to have been the first medical service bureau in the United States.[1] This bureau survived with fluctuatng medical society support until 1925.[2] A detailed account of the evolutionary process is available.[3]

The varied events leading to the rebirth of the King County Medical Service Bureau are as unrecognized by physicians in the 1970's as the organization's potential was by physicians in the 1930's. Today the reestablished Bureau has its own in-house computer system, completely processes all claims submitted and has developed its own utilization and coverage guidelines. A consideration of the Bureau's development may provide a helpful perspective for contemporary health care professionals.

Nationally, organized medicine was disturbed in the 1920's by the growth of group and contract practices, and, late in the decade, by the spread of group hospitalization plans.[4,5] These patterns of delivering medical care were considered "evil" by organized medicine.

In April 1926 a group of prominent leaders of medicine, public health and the social sciences met in Washington, D.C., to consider the changing patterns and inadequacies of medical care. The discussions led to the establishment of the Committee on the Cost of Medical Care, which embarked on a five-year program yielding the first comprehensive study of American health care delivery problems. The Committee concluded its work in 1932 with specific recommendations contained in a majority and two minority reports.[6]

The majority report suggested that medical care should be provided by organized groups of physicians, dentists and other personnel, and that

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medical insurance and taxation should be used to meet the financial burdens of providing medical care. The American Medical Association reacted immediately,[7] endorsing the first minority report which warned against medical "mass production" and the loss of the personal doctor-patient relationship. Both the American Medical Association and the minority report castigated group and contract practices.

Organized medicine in King County had become more and more satisfied with the state of medical practice during the 1920's. Early in the decade, arguments against contract practice appeared with some regularity in *Northwest Medicine*. By mid-1925, though, after the King County Medical Society terminated its original Medical Service Bureau and all its contracts, contract practice was seldom mentioned in either *Northwest Medicine* or *The King County Medical Association Bulletin*. The climax of this trend came in 1929, when contract practice was not mentioned once in either journal.

However, within months after the 1929 stock market crash, the "perennial bugbear"[8] of contract practice again became a primary target for the King County medical profession's vengeance. Thus, economics and ethics were on a showdown course.

Both the King County Medical Society[9] and the Washington State Medical Association[10] established committees to study the contract practice issue, and suggest legislation for its control. The State Association's Committee of Seven or Committee on Economics quickly mailed a questionnaire to all members of the Association, planning to display "the economic conditions of the practice of medicine in the State of Washington,"[11] for the House of Delegates in Seattle in April 1932. The results indicated that contracts were prevalent in 80 percent of the communities represented by the respondees, while nearly 70 percent said they were not in favor of industrial contracts, were opposed to supplemental health contracts and felt that such contracts were harmful to patients and the medical profession. In addition, the Committee noted:

"It is surprising to find out how poorly informed the average doctor is, especially in reference to wage scales, incomes, general costs of living, insurance plans for the sick, what other countries are doing, and what are his legal rights. Transplanted from hospital and medical school to a community, city, or country, he is so busy with clinical practice, digging in and holding on, that he cannot see beyond his own circle, until he suddenly realizes that his income is falling off and he wonders what is the matter. Then he questions and looks around."[11]

With the economic difficulties of the early 1930's pressuring them, many practitioners were beginning to question traditional beliefs. The Committee of Seven assumed from its study that most Washington practitioners would favor a change in their current situations. The Committee, three members of which were from King County, proposed:

"1. Adoption of a new medical practice act and modification of the present medical aid law.

"2. Contracts to be abolished or surrounded by ironclad regulations.

"3. A plan by organized medicine to supply the low income citizens with a fee schedule of insurance sickness (sic) that he can handle."[11]

With regard to the (sic) notation, this may or may not have been a mistake. Although 90 percent of the questionnaire respondees thought that some form of sickness insurance would have been a good adaptation, local and national attitudes of organized medicine toward the subject during the preceding decade could have easily allowed sickness insurance to become "insurance sickness."

The 43rd Annual Meeting of the Washington State Medical Association, held in Tacoma in September 1932, was devoted entirely "to consideration of medical economics,"[12] and the legislative proposals of the Committee of Seven were discussed and endorsed.[13] Within the next several months, a host of bills was prepared by State legislators for the 1932-33 meeting of Washington's state legislature.[14] Organized medicine recognized that it had to compete with other interest groups, so it encouraged all Society physicians to write their representatives. Doctor A. H. Peacock led the encouragement for physician involvement. The climax of this propaganda assault was the publication of the "Declaration of Medical Independence," by Doctor Alexander Hamilton Peacock, MD.[15]

However, the legislature did not meet the expectations of the Washington State Medical Association. The proposed new Medical Practice Act and the associated reestablishment of a State Board of Medical Examiners were defeated. A bill to repeal certain portions of the Workmen's

Compensation Law, and thus do away with the contract system of practice in industry, was also defeated.[16] Clearly, another approach was necessary.

Not all physicians had been willing to wait for legislative action. Beginning in 1930, less critical reports of contract practice appeared.[17] In addition to reading about a successful New York contract practice which was *not* "on a distinctly lower plane than in private practice,"[18] and that the Committee on the Cost of Medical Care had recommended that medical costs "be placed on a group payment basis,"[19] *Northwest Medicine* subscribers learned that the Yakima County Medical Bureau, organized in May 1932, was using a lay business manager to solicit "the signing of contracts with industrial plans."[20] This local development only accentuated similar programs which had begun in 1931 and 1932 in Marion and Multnomah Counties in Oregon, and "at least two county societies" in California.[21] Finally, when the Pierce County Medical Society supported by 80 percent of its membership "launched such an enterprise " in 1932, an editorialist concluded:

". . . The county medical society in some form will supervise contract practice on the part of all members who wish to participate in it, adopting some methods hitherto condemned as unethical but which seem necessary for successful competition with the other contractors."[21]

With the chance for legislative changes seeming remote while economic and peer-group pressures intensified, the King County Medical Society moved to make "medical service insurance a legal and dignified method of self-protection for the wage earning classes and the profession."[22] In February 1933 the Society appointed a Health Insurance Committee to study this suggestion. Not coincidentally, Dr. Morris Fishbein, editor of the *Journal of the American Medical Association,* came to Seattle in March to address the Society. He blasted the Committee on the Cost of Medical Care and contract practices, endorsed the Principal Minority Report of the Committee and admonished the Society to stop medicine's "greatest menace," contract practice, from converting another local medical society to unethical practice.[23] However, Dr. Fishbein's trip was of no avail. Two meetings later, on April 3, 1933, the Society adopted the articles of incorporation of the King County Medical Service Corporation.[24]

The King County Medical Society formed a bureau practice to "distribute the care of the sick among the ranks of its members instead of having it concentrated in the hands of a few."[25] In response to enormous economic pressures, organized medicine expanded the concept of contract practice and allowed a redefinition of its code of ethics. Changes of similar magnitude have occurred in the past and may well occur again as a result of fluctuating economic pressures.

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High Risk Perinatal Care in California

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Rates of perinatal mortality are still too high in California. Mortality and morbidity, particularly for high risk pregnancies, can be reduced by the use of modern technology in the hands of highly trained personnel. New goals for perinatal care have been published by the California Medical Association reflecting these changes. This kind of care is too costly to be developed in all the small obstetric units presently providing services in California. Consolidation of obstetric and neonatal units into fewer hospitals can make it economically possible for these units to meet present-day standards.

INFANT MORTALITY RATES (deaths of infants under one year of age per 1,000 live births), regardless of their limitations and lack of comparability, are used as indicators of the relative development of a society. The 1972 infant mortality figures for developed countries of over 2,500,000 population showed that the United States remained in 16th place with 18.5 deaths per 1,000 live births. Seven states had infant mortality rates as low as or lower than California's 14.8 figure for 1973.[1] Certainly these figures are not acceptable for one of the most highly developed nations in the world or for one of the richest states in that country.

Although maternal mortality in California (1.6 per 10,000 live births in 1973[2]) is among the lowest in the United States, a study of 1,465 maternal deaths in this state from 1958 through 1967 showed that 77 percent of these maternal deaths had one or more avoidable factors, and a disproportionate number of the deaths occurred in black mothers.[3]

It is clear that there is still much that must be done to reduce these mortality figures. In June of 1971 the American Medical Association's House of Delegates formulated a policy on *regionalized* perinatal and intensive care, which said in part, ". . . application of recent advances in scientific knowledge and skills in the intensive care management of high risk pregnant women and high risk newborn infants will result in reduction of present maternal and infant mortality. . . . A major contribution to such a program is the development of centralized community (or regional) hospital based newborn intensive care units. . . . The program's goals should include: 1. programs to identify the high risk pregnancy in sufficient time to allow for delivery at those hospitals which are staffed, equipped and organized for optimal perinatal care." Similar statements have come

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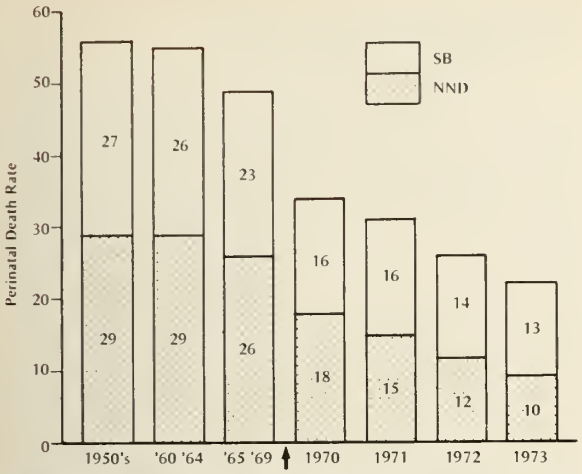

Figure 1.—Perinatal mortality—Los Angeles County/University of Southern California Medical Center. SB (stillborn) signifies fetal death rate (per 1,000 live births), NND is neonatal death rate (per 1,000 live births). Arrow indicates when the neonatal intensive care and aggressive fetal monitoring programs started.

from the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics and the American Academy of Family Practice.

At the Los Angeles County/University of Southern California Medical Center the perinatal death rate was reduced from 41 per 1,000 live births in 1965 through 1969 to 23 per 1,000 live births in 1973.[4] This dramatic drop began in 1970 when fetal monitoring and the newborn intensive care unit were instituted in that facility (Figure 1). Similar drops in perinatal mortality have been reported from hospitals in which newborn intensive care units were installed with and without special high risk obstetric programs.

The Current Perinatal Scene

The rapidly decreasing birth rate has brought about a major crisis in the delivery of maternity and newborn care in California hospitals. There were 362,652 live births in 1970 and less than 300,000 in 1973.[2] Liberalized abortion laws and more adequate family planning services have influenced these birth rates. In 1973 there were 400 abortions for every 1,000 live births to California residents.[5] Although the number of obstetrical units dropped from 424 in 1973 to 385 in 1974, the average occupancy rate for these services remains around 40 percent, far below a rate compatible with optimal function of personnel and equipment and below the break-even point in costs.

At the same time, the whole concept of obstetric and newborn care has undergone a renaissance. Prenatal examination of amniotic fluid now permits the early diagnosis of certain inherited conditions,[6] and parents are counseled about continuing defective pregnancies. Techniques for assessing fetal well-being *in utero* are improving.[7-10] The development of sophisticated fetal monitoring equipment permits more accurate evaluation of fetal distress during labor, and aids in making decisions regarding the kind of intervention needed.[4] The ability to determine fetal lung maturity through amniotic fluid examination for lecithin to sphingomyelin ratios has lowered the risk of respiratory distress in babies born of elective cesarean section or with an elective induction of labor.[11]

The advent and rapid expansion of neonatal intensive care units (NICU) in the late 1960's have revolutionized newborn care for high risk infants. Sophisticated vital function monitoring equipment, assisted ventilation machines, intravenous pumps and infant warmers have been developed and are being constantly modified.

Transport of sick newborn infants, once a matter of using whatever equipment or personnel that could be spared, has become a new science in itself. Specially designed transport incubators with temperature control, monitoring equipment and intravenous pumps in adequately lighted and air conditioned ambulances or aircraft are required. In addition trained teams of neonatal medical specialists, neonatal nurses and social workers may be aboard.

Intensive care equipment is costly to install and maintain, and quickly becomes obsolete. The new technology requires trained personnel to keep the machines operating. Hospital administrators can justify purchase of such items one time. The more important issue of having adequately trained medical, nursing and paramedical personnel available around the clock presents an entirely different problem. Tertiary centers for perinatal care must have highly specialized physicians on the paid staff. These units require a high ratio of nurses to patients, such as one to one in intensive care whether in the labor and delivery or the newborn area. These nurses are also specialists and are continually educated in new techniques. In addition, laboratory, x-ray facilities and respiratory therapists must be available at a few minutes notice around the clock.

TABLE 1.—*California Hospitals by Number of Live Births, 1973**

Number of Live Births Per Year	California Hospitals					
	Total		Rural		Urban	
	Number	Percent	Number	Percent	Number	Percent
0- 250	101	26	62	56	39	14
251- 500	88	23	31	28	57	21
501-1000	98	26	14	13	84	31
1001-2000	71	19	2	2	69	26
>2000	24	6	1	1	23	8
TOTAL	382	100	110	100	272	100

*Births reported for phenylketonuria (PKU) screening.

Another feature of high risk sick newborn care entails family involvement and follow-up. It has been well documented by Klaus[12] and others that interaction between mother and infant is of critical importance in normal child development. Arrangements must be made for parents to become involved early in the care of their sick newborn infants to avoid the barriers between them that are often raised by fear of and isolation from their infant. The graduates from the NICU are at high risk for further difficulties which may be manifested long after discharge. The problems range from higher risk of sudden infant death syndrome and child abuse to neurological, psychological and physical handicaps. It is essential that units caring for these high risk infants have an active follow-up program to prevent these problems or provide treatment, as well as to assess the efficacy of the type of neonatal care that has been given.

While these innovations have greatly reduced perinatal mortality and morbidity, they have also greatly increased the cost of maternity and newborn care. A recent study by the State Department of Health showed that the cost of care for a newborn infant with respiratory distress in 1965 averaged $250 in an ordinary nursery; in 1973 it rose to over $5,000 in an intensive care unit.[13]

The Need for Consolidation and Regionalization

A survey by the American College of Obstetricians and Gynecologists (ACOG) in 1967[14] found that small hospitals delivering less than 500 babies per year lacked many of the services and facilities presently associated with quality perinatal care. These include such items as immediate availability of blood for transfusion, specialized nursing personnel, house staff teaching programs and full-time laboratory back-up. A recent study by Tokukata[15] showed that reduced perinatal mortality was significantly associated with larger obstetrical units, and a higher percentage of occupancy. A study reported by Usher[16] on perinatal mortality by hospital size showed significantly lower mortality figures in hospitals with more than 1,000 live births per year. California data from the ACOG study[14] gave similar results.

Yet, in California in 1973, 75 percent of the hospitals with maternity services had less than 1,000 babies delivered in them and a third of these hospitals averaged under 21 deliveries a month (see Table 1). Even in the urban areas two thirds of the hospitals fell below the optimal delivery level. Comparative delivery figures for Los Angeles for 1970 and 1972 actually showed a downward trend, with the number of hospitals having 1,000 or more deliveries per year dropping from 50 to 42 (Table 2). The births in these smaller services rose from 23 to 30 percent in the two years.

The Perinatal Subcommittee of the Maternal and Child Care Committee of the California Medical Association in conjunction with the State Department of Health developed *Goals for Regionalized Perinatal Care,* published in 1974. This booklet emphasizes the need to establish regional high risk maternity centers and sets standards for such obstetrical units, newborn intensive care

TABLE 2.—*Los Angeles Hospitals by Size Based on Number of Deliveries*

Number of Deliveries	Los Angeles Hospitals				Los Angeles Births			
	1970		1972		1970		1972	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent
< 500	24	22	45	39	6,482	5	13,326	13
501-1000	34	32	27	24	24,036	18	18,215	17
1001-2000	29	27	31	27	40,318	30	40,054	38
>2000	21	19	11	10	64,762	48	34,970	33
TOTAL	108	100	114*	100	135,598	100	106,565	100

*Not including three hospitals where no data were available.

TABLE 3.—*Crippled Children Services Approved Neonatal Units*

FULLY QUALIFIED

Newborn Intensive Care Units

Sacramento Medical Center
Children's Hospital Medical Center, Oakland
Kaiser, Oakland
Children's Hospital, San Francisco
UC Moffitt, San Francisco
Kaiser, San Francisco
Mt. Zion, San Francisco
Stanford University Medical Center
Santa Clara Valley, San Jose
Bauer Hospital, St. Mary Medical Center, Long Beach
Cedars, Los Angeles
UCLA, Los Angeles
LAC/USC, Los Angeles
Children's Hospital, Los Angeles
Martin Luther King, Jr., Los Angeles
Harbor General, Torrance
Memorial Medical Center and Children's Hospital, Long Beach
Children's Hospital of Orange County, Orange
Orange County Medical Center, Orange
Loma Linda University Medical Center
Valley Children's, Fresno
Children's Hospital, San Diego
University Hospital, San Diego

INTERMEDIATE

Infant Intensive Care Units

Marin General, Greenbrae
Santa Rosa Memorial
Sutter Memorial Hospital, Sacramento
Valley Medical Center, Fresno
General Hospital Ventura County, Ventura
Kaiser, Santa Clara
San Bernardino General
Riverside General
Mercy Hospital, Redding
Little Company of Mary, Torrance
Huntington Memorial, Pasadena
Queen of the Valley, West Covina
Presbyterian Intercommunity, Whittier
St. Francis, Lynwood
Pomona Valley Community, Pomona
Valley Presbyterian Hospital, Van Nuys
Washoe Medical Center, Reno

units and transport of sick infants. It also includes goals for maternity and newborn services in intermediate level community hospitals.

Efforts are being made to develop a method for accurately identifying high risk pregnancies early in the course of prenatal care.[17] Most authorities agree that only about half of such pregnancies can be predicted in the prenatal period. The remaining high risk conditions will become manifest during labor and delivery. Therefore, *all* hospitals providing delivery services must be prepared to deal with unexpected emergencies in order to prevent a disaster.

At present the existence and distribution of specialized perinatal services in California is less than optimal. Very few centers are set up specifically to care for high risk pregnancies and deliveries. There are more newborn intensive care units. The California Crippled Children Services has approved 23 as fully qualified NICU's and 17 intermediate facilities throughout the state (Table 3). Six approved newborn intensive care units are in Los Angeles County with over 100,000 live births annually and four are in San Francisco County with 14,000 live births per year. But vast geographical areas of the state are totally uncovered and large population centers are not covered adequately.

The use of the present neonatal centers is increasing notably.[13] Recently there has been a serious shortage of intensive care bassinets, even in the San Francisco area which had been considered over-bedded. If this trend continues it will be necessary to drastically adjust upward the present estimates of need for neonatal intensive care beds.

Conclusions

Every hospital in the state with maternity and newborn services must be equipped and have personnel trained to handle unexpected high risk patients, at least long enough for safe transfer to perinatal centers. This will require consolidation of services into larger units with enough deliveries to offset the cost of these added services. Remote rural community hospitals require special individual consideration. Perinatal centers offering complete high risk maternity and newborn services must be developed so that they are available within easy transport distance to all mothers delivering in the state. It is essential that every community hospital with a maternity service develop a liaison with a high risk center for consultation, for education of medical and nursing staff and as an ultimate source of care when the community hospital cannot cope with certain problems.

Consolidation of maternity services has become both a functional and a fiscal necessity. In spite of this fact, few communities have succeeded in bringing this about. For a variety of reasons, small competing obstetrical units continue to operate with a declining level of services and expertise. It is urgent that the health providers in each community face the issue of maternity-care consolidation, if the standard of maternity and newborn services in California is to be improved.

This will mean that disparate groups in each community must look critically and objectively at the hospital and local health care system. Facilities best qualified to provide each type of specialized service should be encouraged to continue while those not qualified should be encouraged to cease that particular function. Just as it is ridiculous to expect every hospital to provide for renal dialysis or open heart surgical procedures, it is no longer rational to expect every hospital to provide complete maternity and newborn services, which have in recent times become just as specialized.

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Podophyllum Fluid Extract in the Management of Condylomata

I use fluid extract and vanishing cream . . . You must specify to the pharmacist that you want fluid extract (25 percent) in vanishing cream, because otherwise he will put powdered podophyllum in vanishing cream and it does not have enough strength to come in out of the rain . . . Fluid extract is ten times stronger than the powder so you must make it fluid extract even if it does not make any difference how you are going to put it up—whether you are going to put it in mineral oil, shellac or vanishing cream. It is just handy to put it in vanishing cream because it is easy to use and stays where you put it.

—IVAN I. LANGLEY, MD, *Portland, OR*
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A Survey of Physician Participation in and Dissatisfaction with the Medi-Cal Program

MICHAEL W. JONES, MBA, *and* BETTE HAMBURGER, BA, *San Francisco*

A Socioeconomic Report of the Bureau of Research and Planning
California Medical Association

In late 1974, the California Medical Association's Bureau of Research and Planning sent questionnaires about participation in Medi-Cal (California's Medicaid program) to a random sample of 1,200 members in private medical practice. Questions covered degree of current participation in the program; plans for future participation; patterns of acccptance of new Medi-Cal patients, referrals and consultations, and similar questions about personal involvement in the program. Responses were received from almost 70 percent of physicians sampled.

Subsequently, respondents who have curtailed participation in Medi-Cal or plan to do so were sent a follow-up questionnaire to elicit information about their perception of various problem areas within the program. From these data, evaluations can be made concerning the types of reform that might be most fruitful in eliciting the broad-scale physician participation on which the program is conceptually based. Well over three-quarters of the 336 physicians in this subsample group provided data.

These findings represent highlights of a detailed report, single copies of which are available on request from the CMA's Division of Research and Socioeconomics.

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Part I—The Broad-Scale Sample

Most Physicians Participate in Medi-Cal Program

As seen in Table 1, approximately one patient in ten (9.7 percent) being treated by the average physician is covered under the Medi-Cal program. However, the table clearly shows that a substantial number of physicians (14.9 percent) practice in a situation where over a quarter of all their patients are under Medi-Cal, while a relatively small proportion (6.3 percent) treat no Medi-Cal patients whatever. More than a fourth of all respondents (25.6 percent) conduct practices in which fewer than 5 percent of their patients are on Medi-Cal.

Understandably, participation differs according to medical specialty. Pediatricians tend to have a relatively higher proportion of Medi-Cal patients than do most other physicians, while internists, obstetrician/gynecologists and orthopedists have below-average proportions. Many pediatricians, general practitioners and psychiatrists have a patient load of which more than a fourth is made up of Medi-Cal patients. At the other end of the spectrum, above average proportions of obstetrician/gynecologists and psychiatrists treat no Medi-Cal patients whatever. One psychiatrist, who formerly treated Medi-Cal patients, commented that he would participate "only if Medi-Cal patients would be permitted as many visits as were necessary to help them."

TABLE 1.—*Proportion of Total Patients Covered Under Medi-Cal, by Medical Specialty, January 1975*

Specialty	Total Respondents		Proportion of Patients Under Medi-Cal: None		Under 5%		5-10%		11-15%		16-25%		Over 25%		Medi-Cal Patients Taken by Avg. Practitioner
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Percent
General/Family Practice	160	100	5	3.1	38	23.8	35	21.9	22	13.8	21	13.1	39	24.4	10.9
Internal Medicine[1]	126	100	6	4.8	47	37.3	32	25.4	23	18.3	9	7.1	9	7.1	6.7
Pediatrics[1]	41	100	0	..	5	12.2	9	22.0	10	24.4	5	12.2	12	29.3	13.7
Other Medical[2]	31	100	2	6.5	8	25.8	7	22.6	7	22.6	4	12.9	3	9.7	9.3
General Surgery[3]	57	100	2	3.5	16	28.0	12	21.0	16	28.0	7	12.3	4	7.0	9.8
Other Surgery[4]	32	100	2	6.3	9	28.1	4	12.5	6	18.8	9	28.1	2	6.3	11.3
Obstetrics/Gynecology	59	100	7	11.9	23	39.0	7	11.9	8	13.6	8	13.6	6	10.2	5.0
Ophthalmology	37	100	1	2.7	8	21.6	9	24.3	8	21.6	8	21.6	3	8.1	10.8
Orthopedic Surgery	35	100	3	8.6	12	34.3	7	20.0	4	11.4	8	22.9	1	2.9	7.0
Otolaryngology	19	100	0	..	6	31.6	3	15.8	4	21.1	4	21.1	2	10.5	11.4
Psychiatry[1]	58	100	8	13.8	9	15.5	12	20.7	6	10.3	10	17.2	13	22.4	10.5
All Other	35	100	9	25.7	7	20.0	7	20.0	3	8.6	7	20.0	2	5.7	6.2
Total (excluding Anesthesiology, Radiology and Pathology)[5]	690	100	45	6.5	188	27.2	144	20.9	117	17.0	100	14.6	96	13.9	9.3

[1]Including subspecialties.
[2]Includes allergy, dermatology, neurology, physical medicine.
[3]Includes abdominal surgery, colon and rectal surgery, pediatric surgery.
[4]Includes cardiovascular surgery, neurological surgery, plastic surgery, thoracic surgery, urology.
[5]Excludes two respondents who did not answer this specific question.

Generally, however, the table suggests that Medi-Cal patients are reasonably well distributed among physicians, since in the aggregate very few physicians have no Medi-Cal patients and relatively few have practices dominated by Medi-Cal patients.

Few Respondents Want More Medi-Cal Patients

Table 2 provides information about patterns of acceptance of new Medi-Cal patients, according to medical specialty. Data from anesthesiologists, radiologists and pathologists have been excluded, since they are generally unable to make an independent decision about whom they treat. Also excluded are data from respondents who have never treated Medi-Cal patients. Among other respondents, 43.1 percent probably would accept a new Medi-Cal patient, 19.9 percent might accept one, 24.6 percent probably would not accept one and 12.4 percent definitely would not accept a new Medi-Cal patient. Thus, it is clear that only a minority of California's private practitioners would willingly provide care to a new Medi-Cal patient seeking their services if the circumstances were such that they could make such a choice.

Data about physician willingness to accept new Medi-Cal patients according to their current level of participation are also shown in Table 2. Excluded from this portion of the table are respondents who indicated that they have never treated patients under the program; included, however, are anesthesiologists, radiologists and pathologists.

The data show a close association between degree of current Medi-Cal involvement and willingness to continue treating patients under the program. Among physicians whose case load is currently over a quarter Medi-Cal patients, almost four out of five respondents (79.8 percent) indicated that they probably would accept a new Medi-Cal patient who requested care, while just over 10 percent indicated that they either probably or definitely would not accept a new Medi-Cal patient seeking services at this time.

At the low end of the spectrum of current Medi-Cal participation, more than six out of ten respondents (63.4 percent) indicated that they probably would not or definitely would not accept a new Medi-Cal patient, while fewer than a fourth (22.8 percent) said that they probably would accept one. This close association suggests that the base of Medi-Cal participation by California

TABLE 2.—*Acceptance of New Medi-Cal Patients, by Medical Specialty and Level of Current Involvement in the Program*

Specialty/Level of Current Participation	Total Respondents		Acceptance of New Medi-Cal Patients: Probably Would		Might		Probably Not		Definitely Not	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
General/Family Practice	155	100	52	33.5	32	20.6	37	23.9	34	21.9
Internal Medicine[1]	121	100	30	24.8	23	19.0	51	42.1	17	14.1
Pediatrics[1]	41	100	23	56.1	11	26.8	5	12.2	2	4.9
Other Medical[2]	31	100	18	58.1	3	9.7	8	25.8	2	6.5
General Surgery[3]	57	100	32	56.1	11	19.3	10	17.5	4	7.0
Other Surgery[4]	32	100	18	56.3	7	21.9	6	18.8	1	3.1
Obstetrics/Gynecology	57	100	24	42.1	13	22.8	16	28.1	4	7.0
Ophthalmology	37	100	28	75.7	3	8.1	4	10.8	2	5.4
Orthopedic Surgery	33	100	10	30.3	6	18.2	11	33.3	6	18.2
Otolaryngology	19	100	13	68.4	6	31.6	0	..	0	..
Psychiatry[1]	54	100	24	44.4	13	24.1	10	18.5	7	13.0
All Other	26	100	14	53.8	4	15.4	5	19.2	3	11.5
Total (excluding Anesthesiology, Radiology and Pathology)[5]	663	100	286	43.1	132	19.9	163	24.6	82	12.4
Formerly treated, none now	24	100	1	4.2	1	4.2	9	37.5	13	54.2
Under 5 percent	189	100	43	22.8	34	18.0	77	44.9	35	18.5
5 to 10 percent	156	100	66	42.3	35	22.4	35	22.4	20	12.8
11 to 15 percent	127	100	62	48.8	33	26.0	22	17.3	10	7.9
16 to 25 percent	109	100	69	63.3	20	18.3	15	13.8	5	4.6
Over 25 percent	109	100	87	79.8	11	10.1	7	6.4	4	3.7
Total[6]	714	100	328	45.9	134	18.8	165	23.1	87	12.2

[1-4]See footnotes to Table 1.
[5]Excludes 23 respondents who have *never* treated Medi-Cal patients, and 8 who did not respond to this specific question.
[6]Excludes physicians who have *never* treated any Medi-Cal patients.

TABLE 3.—*Physicians' Continued Treatment of Current Medi-Cal Patients During the Coming Year by Medical Specialty and Level of Current Involvement in the Program*

Specialty/Level of Current Participation	Total Respondents		Treatment of Current Medi-Cal Patients: Continue, Plus Family Members		Continue Patients Only		Gradually Lower Number of Patients		Curtail Number of Patients Soon	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
General/Family Practice	154	100	98	63.6	27	17.5	22	14.3	7	4.5
Internal Medicine[1]	119	100	46	38.7	41	34.5	21	17.6	11	9.2
Pediatrics[1]	41	100	32	78.0	6	14.6	2	4.9	1	2.4
Other Medical[2]	29	100	16	55.2	8	27.6	4	13.8	1	3.4
General Surgery[3]	55	100	32	58.2	10	18.2	9	16.4	4	7.3
Other Surgery[4]	30	100	17	56.7	3	10.0	7	23.3	3	10.0
Obstetrics/Gynecology	52	100	25	48.1	12	23.1	11	21.1	4	7.7
Ophthalmology	36	100	29	80.6	3	8.3	3	8.3	1	2.8
Orthopedic Surgery	31	100	10	32.3	10	32.3	9	29.0	2	6.5
Otolaryngology	19	100	18	94.7	0	..	1	5.3	0	..
Psychiatry[1]	49	100	26	53.1	7	14.3	13	26.5	3	6.1
All Other	26	100	11	42.3	4	15.4	7	26.9	4	15.4
Total (excluding Anesthesiology, Radiology and Pathology)[5]	641	100	360	56.2	131	20.4	109	17.0	41	6.4
Under 5 percent	190	100	76	40.0	61	32.1	27	14.2	26	13.7
5 to 10 percent	156	100	92	59.0	27	17.3	30	19.2	7	4.5
11 to 15 percent	126	100	74	58.7	26	20.6	21	16.7	5	4.0
16 to 25 percent	109	100	67	61.5	12	11.0	25	22.9	5	4.6
Over 25 percent	110	100	86	78.2	9	8.2	13	11.8	2	1.8
Total[6]	691	100	395	57.2	135	19.5	116	16.8	45	6.5

[1-4]See footnotes to Table 1.
[5]Excludes 23 respondents who have never treated Medi-Cal patients, 24 who have no current Medi-Cal patients, and 7 who did not respond to this specific question.
[6]Excludes physicians with no Medi-Cal patients currently under their care.

TABLE 4.—*Medi-Cal Patient Load Expected in Three Years, by Current Level of Program Participation*

Proportion of Patients Under Medi-Cal	Total Respondents		Proportion of Medi-Cal Patients in Three Years							
			Larger		Same		Smaller		No Answer	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Under 5 percent	191	100	14	7.3	99	51.8	72	37.7	6	3.1
5 to 10 percent	158	100	18	11.4	97	61.4	42	26.6	1	0.6
11 to 15 percent	129	100	24	18.6	66	51.2	36	27.9	3	2.3
16 to 25 percent	109	100	33	30.3	57	52.3	19	17.4	0	—
Over 25 percent	111	100	40	36.0	46	41.4	23	20.7	2	1.8
Total[1]	698	100	129	18.5	365	52.3	195	27.5	12	1.7
No Medi-Cal Patients Currently Under Care	47	100	3	6.4	44	93.6	0	0.0	0	0.0

[1]Excludes physicians with no Medi-Cal patients currently under their care.

physicians is gradually narrowing and that, absent program changes, the future will find fewer physicians treating more patients under the program.

Many Plan to Curtail Medi-Cal Involvement

Table 3 provides information about the future plans of physicians who are currently treating Medi-Cal patients. Most physicians indicated that they will continue treating Medi-Cal patients, as well as family members. However, a substantial proportion (17.0 percent) intend gradually to lower the number of Medi-Cal patients under their care, while some others (6.4 percent) plan to curtail caring for Medi-Cal patients as rapidly as feasible.

Internists and orthopedists showed particular reluctance to offer services to "family members" not currently under their care. "Other" surgeons, such as neurosurgeons and urologists, obstetrician/gynecologists, orthopedists and psychiatrists seem especially anxious to lower the proportion of Medi-Cal patients under their care. This proposed course of action was noted by very few pediatricians, ophthalmologists or otolaryngologists.

Information about future plans regarding Medi-Cal participation according to level of current involvement by physician respondents is also contained in Table 3. Most physicians with significant current involvement expect to remain involved, while those with a low level of participation plan to limit their participation even more or, in fact, curtail it entirely. The data again show that the base of physicians available to provide care under the program is narrowing and that relatively more care will be provided in the future by those physicians who already have significant involvement in the program.

Further Evidence of Narrowing Base

As seen in Table 4, most respondents (52.3 percent) indicated that they expect the proportion of Medi-Cal patients under their care in three years to be similar to the current proportion. Among others, 27.5 percent plan to be treating a smaller proportion. Since it is unlikely that many respondents expect the program itself to contract, one can assume that this group of respondents propose to achieve a diminished proportion by reason of their own voluntary actions with respect to participation in the program.

While only 7.3 percent of physicians whose current case load is under 5 percent Medi-Cal expect to increase this proportion, almost two in five (37.7 percent) plan to reduce it. Conversely, among those physicians whose current complement of patients is over a fourth Medi-Cal, well over a third (36.0 percent) expect to be treating an even larger proportion in the future, while only one in five (20.7 percent) expect the proportion to diminish.

Although the association between these two variables is extremely close, it should also be noted that a small but nonetheless significant proportion of physicians who are heavily involved in the program apparently wish to curtail their degree of involvement. The data also suggest that an almost negligible proportion of physicians not currently treating any Medi-Cal patients expect to begin participating in the program in the future.

Although not shown in Table 4, among physicians who expect to be treating relatively more Medi-Cal patients, an overwhelming majority indicated that this is based on their own feeling of responsibility. Many also anticipate that more Medi-Cal patients will be seeking a new physician in the future. Relatively few physicians considered

TABLE 5.—*Respondent Ratings of Various Potential Problem Areas in the Medi-Cal Program*

Problem Area	Total Responding[1]		Seriousness of Problem: Critical		Major		Minor		Not a Problem	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Inability to determine amount MD will be paid	243	100	57	23.5	109	44.9	62	25.5	15	6.2
Excessive paperwork	249	100	92	36.9	101	40.6	52	20.9	4	1.6
Delays in payment	243	100	73	30.0	83	34.2	66	27.2	21	8.6
Difficulty in securing prior authorization	230	100	43	18.7	83	36.1	70	30.4	34	14.8
Inadequate level of reimbursement	244	100	125	51.2	90	36.9	26	10.7	3	1.2
Denial of reimbursement for services provided	231	100	107	46.3	81	35.1	27	11.7	16	6.9
Bureaucratic interference with patient care	242	100	111	45.9	66	27.3	40	16.5	25	10.3

[1]Excludes physicians who indicated "don't know" or who did not respond to specific portions of the question.

the program "reasonably easy to work with," while an almost negligible proportion indicated a preference for Medi-Cal patients to other types of patients. Almost half of these respondents expected that they would be treating a larger proportion of Medi-Cal patients because other physicians in their geographic area are limiting their Medi-Cal practice.

Part II—The Follow-Up

Who Provided the Data

Information contained in the follow-up survey is based on responses from a sample of 336 California Medical Association members who, in answer to Part I of the "Medi-Cal Participation Survey," indicated that they either treat no patients under the Medi-Cal program or had cut back on their participation or planned to do so in the future. This represents 45 percent of the total group of physicians who responded to the earlier questionnaire.

Usable responses were received from 258 of the 336 physicians sampled, or 76.8 percent. This high rate of response assures that the data represent with reasonable accuracy the opinions of physicians sufficiently alienated by Medi-Cal to have taken action with respect to their own personal participation in the program.

Medi-Cal Problem Areas Identified

Table 5 indicates how respondents rated various potential problem areas within the Medi-Cal program. Over half of all respondents (51.2 percent) consider inadequate level of reimbursement a critical problem to them with reference to participation in the Medi-Cal program. Almost as important are the problems of denial of reimbursement for services already provided and bureaucratic interference in patient care. Totals of 46.3 and 45.9 percent, respectively, called these problems "critical." Interestingly, a total of 26.8 percent of respondents considered bureaucratic interference only a minor problem or not a problem at all in the program.

Excessive paperwork was rated as a critical problem by well over a third of all respondents (36.9 percent) and a major problem by another two fifths (40.6 percent). Combining these two categories, in fact, results in an evaluation that this problem is more important than that of bureaucratic interference in patient care.

Slightly lower in severity are the delays experienced by physicians in receiving payment for services and their inability to determine the amount they will be paid for services. Approximately two thirds of all respondents consider each of these problems either critical or major. With reference to delays, a gastroenterologist in Orange County commented:

> We have a deadline of 2 months to get our claims in, yet we have claims that have not been paid by Medi-Cal for over a year. When inquiries are sent, we receive a letter—"Claims are being processed. No further inquiries needed."

An obstetrician/gynecologist in the same community, concerned with the problem of being able to determine how reimbursements are based, said:

> Doctors receive different fees for obstetrical care even though all have charged the same. There is a $41 difference depending on the doctor billing. We have contacted the representative and submitted documentation as requested but never receive answers to our inquiry.

Lowest ranked among the seven suggested

problem areas is that of difficulties experienced by physicians in securing prior authorization to provide care. Well over half of all respondents consider this problem critical in nature, however, while just over 14.8 percent indicated it is not a problem for them. In obvious frustration, a Los Angeles general practitioner remarked:

> To sit on the phone for 45 minutes to get authorization is an unbelievable waste of time!

Who Rates Which Situations "Critical"

Some of the more crucial problems showed an association with specific variables such as medical specialty or geographic area in which physicians practice. Although detailed data concerning these relationships cannot be included in this report, the following highlights are extracted from the full report of findings.

The problem of inadequate level of reimbursement under Medi-Cal is considerably more critical for surgeons of all types and somewhat more so for psychiatrists than for other types of physicians. A Los Angeles orthopedic surgeon, for example, provided the following example:

> I adjusted my accounts down over $900 on my usual and customary fees in January 1975; these were all Medi-Cal patients.

A San Francisco neurosurgeon commented:

> A professional responsibility is increasing relative to my patients, the financial return is getting less and less for my efforts at patient care. I receive approximately 60 cents return for every $1 billed for Medi-Cal patients, with no increase in my fees in 5 years.

Although the factor of difficulty in securing prior authorization ranked lowest in overall terms, it is nonetheless relevant and data concerning its association with medical specialty and with geographic area are of importance in evaluating the functioning of the program.

Physicians in the fields of neurosurgery, plastic surgery, thoracic surgery, urology, internal medicine (including its subspecialties), "other" medical specialties (dermatology, allergy, pediatrics) and psychiatry consider this more of a problem than do other physicians. A psychiatrist from Santa Clara County said, for example:

> My practice is largely concerned with long term psychotherapy. Authorization is given for short times and I must watch expiration dates and submit new requests or lose payment. This situation plus the uncertainty of obtaining continuing authorizations more than any other reason causes me to limit my participation.

The problem of denial of reimbursement for services already provided appears to be particularly acute among certain surgical specialties, such as general surgery, ophthalmology, otolaryngology and orthopedic surgery. Almost all internists called it either critical or major. An Orange County otolaryngologist commented, for example:

> We have recently written off over $400 of services which were authorized but have never been paid even after all of the initial paperwork and the follow-up work.

Almost half of general and family practitioners (49.2 percent) consider this problem critical. One general practitioner from San Diego, who no longer accepts Medi-Cal patients, stated:

> During my last year of real participation, two-thirds of bills were denied after service rendered, even though prior authorization was obtained. Entire program has been handled by state officials in an arbitrary and unreasonable and incompetent manner.

The problem of excessive paperwork appears to be considered more critical by surgeons than by physicians in medical specialties. A substantial majority of ophthalmologists, otolaryngologists, orthopedic surgeons and general surgeons consider this problem either critical or major. On the other hand, relatively fewer internists, physicians in "other" medical specialties (pediatrics, dermatology, allergy) and in "other" surgical specialties (neurosurgery, plastic surgery, thoracic surgery, urology) consider the problem critical.

TABLE 6.—*Respondent Agreement or Disagreement with Various Statements Concerning Effects of the Treatment Authorization Request (TAR) System*

	Total Responding[1]		Response			
			Agree		Disagree	
Statement	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
Treatment is often delayed	186	100	144	77.4	42	22.6
System interferes with case management	186	100	153	82.3	33	17.7
Follow-up care reduced or denied	177	100	128	72.3	49	27.7
Inconsistencies due to ill-defined criteria	165	100	141	85.5	24	14.5
Needed treatment is often denied	166	100	90	54.2	76	45.8

[1]Excludes physicians without a TAR requirement in their area and those who indicated "don't know" or who did not respond to specific portions of question.

Other Insights into Problem Areas

The full report of findings also provides information about problem areas physicians consider most serious within the program, according to medical specialty, geographic area and current degree of involvement in Medi-Cal. The following are some highlights:

• Ophthalmologists, otolaryngologists, orthopedic surgeons, psychiatrists, physicians heavily involved in Medi-Cal and physicians who *are* willing to accept new Medi-Cal patients are particularly concerned about excessive paperwork requirements. One psychiatrist put it this way:

> When considering that I do not get my usual fee, and that I do not get paid for the time spent in the enormous amount of paperwork required, I conclude that I provide an awful lot of free service. I am willing to do this for patients with whom I have developed a physician-patient relationship before they went on Medi-Cal, but not otherwise.

• Low levels of physician reimbursement are considered especially critical by general surgeons, obstetrician/gynecologists, orthopedic surgeons, practitioners in Orange County, San Diego County, and the west Bay Area, and physicians who plan to accept no new Medi-Cal patients. As a Los Angeles internist said:

> I would be glad to do the paperwork, carry the accounts receivable (often 9 to 12 months) if my secretary's time were reimbursed and my usual and customary fee were paid. But $6 for an office visit and $7 for a 2 a.m. emergency room visit is ridiculous if the patient takes more than 3 to 5 minutes of my time.

• Retroactive denial of reimbursement is particularly critical to physicians in "other" medical specialties (pediatrics, dermatology, etc.), to physicians in the Bay Area and in Orange County, and to physicians who plan to continue accepting new Medi-Cal patients. A general surgeon from San Bernardino County noted the following:

> Our major problem is in emergency surgery cases with retroactive authorization. The hospital is usually paid. The surgeon is rarely paid. We have no choice other than treat people and I feel we should have at least some pay.

• Bureaucratic interference in patient care constitutes a special problem for general and family practitioners, ophthalmologists, otolaryngologists, "other" surgeons (neurosurgery, plastic surgery, thoracic surgery, urology), physicians in Los Angeles County, physicians who do not treat Medi-Cal patients and those who indicated that they only "might" accept a new Medi-Cal patient for care. One Los Angeles psychiatrist made this observation:

> I can understand the need to restrict certain care, but it is to painful for me to have to deny a patient after we have started the program.

TAR's Cause Several Concerns

Table 6 provides information about respondent opinion concerning the effect of the treatment authorization request (TAR) system. Respondents were asked to agree or disagree with each of five possible effects of the system in terms of its pertinence to their own particular experience with the Medi-Cal program.

Among those who were sufficiently familiar with the system to respond, the area of concern with which most agreed (85.5 percent) was that the system results in "inconsistencies due to apparently ill-defined criteria." A psychiatrist from San Diego said: "Since the Medi-Cal rules fluctuate, the procedures are unclear and require excessive amounts of time to unravel."

Significant proportions of physicians also felt that the system interferes with case management (82.3 percent), that treatment is often delayed (77.4 percent) and that appropriate follow-up care is often reduced or denied (72.3 percent). Regarding the problem of follow-up care, one orthopedic surgeon from Orange County said:

> A major problem in orthopedics is obtaining adequate post injury or post operative physical therapy —enough of a problem that the patient is better off being referred to a county facility for any surgical procedure which requires post-op. therapy.

Only a slight majority (54.2 percent) agreed with the proposal that "needed treatment is often denied." However, there was little consistency in the thinking of respondents with respect to this issue. Although not shown in the tabular data, certain associations between this problem and medical specialty, as well as geographic area, appear to exist.

The problem of treatment denial is particularly prevalent among internists, psychiatrists and physicians in "other" medical specialties such as dermatology and pediatrics, as well as among general and family practitioners. A Los Angeles cardiologist commented, for example:

> The biggest problem I face is the statutory limitation on the kinds and amounts of service I can render. Most of my patients are chronically ill with multiple system disease. On a full day I see maybe 8 to 10 people. This is so out of phase with what Medi-Cal will allow, that I will not work with a Medi-Cal recipient unless I have some personal commitment to that person or their family.

TABLE 7.—*Frequency with Which Respondents Experience Retrospective Denial Resulting in Nonpayment for Services Rendered to Medi-Cal Patients, According to Medical Specialty*

	Total Responding[1]		Frequency of Occurrence							
			Frequently		Occasionally		Seldom		Never	
Medical Specialty	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
General/Family Practice	55	100	19	34.5	24	43.6	8	14.5	4	7.3
Internal Medicine[2]	47	100	16	34.0	25	53.2	3	6.4	3	6.4
Other Medicine[3]	17	100	3	17.6	7	41.2	5	29.4	2	11.8
General Surgery[4]	13	100	4	30.8	5	38.5	3	23.1	1	7.7
Obstetrics/Gynecology	12	100	3	25.0	6	50.0	3	25.0	0	..
Ophthalmology/ Otolaryngology	9	100	2	22.2	7	77.8	0	..	0	..
Orthopedic Surgery	15	100	2	13.3	6	40.0	5	33.3	2	13.3
Other Surgery[5]	12	100	3	25.0	6	50.0	1	8.3	2	16.7
Psychiatry	20	100	2	10.0	11	55.0	5	25.0	2	10.0
All Other	9	100	0	..	7	77.8	2	22.2	0	..
Total	209	100	54	25.8	104	49.8	35	16.7	16	7.7

[1]Excludes physicians without a TAR requirement in their area and those who indicated "don't know" or who did not respond to specific portions of question.
[2]Includes subspecialties.
[3]Includes allergy, dermatology, neurology, physical medicine.
[4]Includes abdominal surgery, colon and rectal surgery, pediatric surgery.
[5]Includes cardiovascular surgery, neurological surgery, plastic surgery, thoracic surgery, urology.

TABLE 8.—*Respondent Opinion Concerning Medical Advisors Within the Medi-Cal System, According to Selected Areas and for the State*

	Total Responding[1]		Opinion[2]									
			Understanding		Fair		Inconsistent		Arbitrary		Dollar Oriented	
Geographic Area	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
Alameda/ Contra Costa	20	100	6	30.0	4	20.0	4	20.0	3	15.0	3	15.0
Los Angeles	66	100	11	16.7	11	16.7	16	24,2	9	13.6	19	28.8
Orange	18	100	3	16.7	4	22.2	7	38.9	2	11.1	2	11.1
San Diego	12	100	6	50.0	2	16.7	2	16.7	0	..	2	16.7
Santa Clara	16	100	6	37.5	1	6.2	4	25.0	2	12.5	3	18.8
Riverside/ San Bernardino	10	100	5	50.0	0	..	2	20.0	0	..	3	30.0
Other Areas	55	100	21	38.2	6	10.9	12	21.8	3	5.5	13	23.6
Total State	197	100	58	29.4	28	14.2	47	23.9	19	9.6	45	22.8

[1]Excludes physicians who did not respond to specific question. [2]See text for full content of statements.

With respect to geographic area, almost four out of five respondents in Los Angeles County acknowledged a problem of treatment denial. Conversely, the situation appears much less prevalent in areas such as San Diego, Santa Clara, Riverside and San Bernardino Counties, as well as in counties where there were too few respondents to permit individual identification. In most cases, these counties are smaller metropolitan areas or rural areas.

Several respondents commented that they try to avoid the necessity of securing a TAR, often merely absorbing the cost of providing the service. As one Los Angeles internist put it:

> We do not ask for TAR unless absolutely necessary. We cannot turn a seriously ill patient away so we see them whether we receive payment for the treatment or not. We feel this is an unfair situation.

Many Experience Retrospective Denial

Table 7 relates to the problem of retrospective denial and how frequently it results in nonpayment for services already provided, according to medical specialty. Among all respondents, slightly over a fourth (25.8 percent) indicated that they often experience retroactive denial, while almost half (49.8 percent) indicated that they experience it occasionally. The remaining respondents stated that the problem seldom (16.7 percent) or never (7,7 percent) occurs.

Over a third of respondents in general and family practice (34.5 percent) and in internal medicine (34.0 percent) indicated that the problem often occurs, while relatively few orthopedic surgeons (13.3 percent) or psychiatrists (10.0 percent) have experienced this situation. An ex-

ample of the frustrations physicians experience in securing payment for services already provided are the following comments of a Los Angeles internist:

> The most galling factor is as follows: a bill is submitted by this office for Medi-Cal services. Many months go by . . . no answer. A follow-up tracer letter is written asking for payment. Again many months go by. Finally 2 payments are made for 2 months, and 2 payments for 2 visits during earlier months are not. Attempts to receive explanation by long distance telephone, correspondence (from Los Angeles to San Francisco) is like putting your body into a barrel of taffy. The harder you try, the more involved you get. The stupid answers one gets from the retarded personnel employed by Medi-Cal is enough to raise my renin-angiotensin levels to astronomical heights. Finally, in desperation and total frustration, I hang up, turn to my secretary and state: "Write the damn unpaid bill off and don't take any more Medi-Cal patients." . . . and that's where it stands today. It is amazing how efficiently that Medicare bills are paid and how promptly I receive answers to any inquiries I might make.

Medical Advisors Elicit Mixed Reactions

Table 8 provides information about respondent opinion of medical advisors within the Medi-Cal system according to geographic area. Among all respondents, most felt that medical advisors were at best inconsistent in handling requests for authorization. As one general practitioner commented: "Personal idiosyncrasies of the medical consultant are impossible to overrule." A substantial minority (22.8 percent) felt that advisors appear more concerned with the money than with patient care, while a considerably smaller but nevertheless significant group (9.6 percent) indicated that advisors are often arbitrary in dealing with requests for authorization. At the other end of the spectrum, almost three respondents in ten (29.4 percent) felt that medical advisors are generally understanding and willing to authorize recommended treatment, while another large group (14.2 percent) were of the opinion that medical advisors are fair but stringent in providing treatment authorization. A family practitioner from San Diego expressed the feeling that advisors are "hamstrung by state regulations."

Respondents in Los Angeles County were particularly critical of medical advisors, while those in Alameda, Contra Costa, Orange and San Diego counties appeared to be somewhat less critical. Almost two respondents in five from Orange County (38.9 percent) indicated that advisors are inconsistent in handling requests for authorization. In San Diego and in the Riverside-San Bernardino area, however, half of all respondents indicated that advisors are "generally understanding."

Although not shown in the tabular data, findings show that there is only a limited degree of association between physician opinions about medical advisors and medical specialty. However, physicians in strictly medical specialties (internal medicine, pediatrics, dermatology and so forth) tend to be somewhat more critical of medical advisors or of the system, than do physicians in most other specialties. An internist in Santa Clara County said:

> It is seldom that we are able to communicate with the medical advisor personally. Most requests are relayed to him (and his questions to me) through a clerk who has little medical knowledge.

A General Practitioner Sums It Up

Summing up various concerns with the Medi-Cal program experienced by physicians, especially those with considerable involvement in the program, one general practitioner from Alameda County made the following comments:

> I practice in a high Medi-Cal area, and I refuse three or four new Medi-Cal patients per week. I quit taking new patients when the total came to 25 percent of my practice. Since my expenses are about 50 percent of my receipts, I felt very uneasy about having half of my personal income dependent on Medi-Cal, to be reduced or deferred as they see fit.
>
> I would accept more Medi-Cal patients if I could feel that the program was dedicated to fair treatmen of both patient and doctors.

in memoriam

ARTHURS, ELIZABETH, San Francisco. Died October 7, 1975 in West Chester, Pennsylvania, aged 81. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1921. Licensed in California in 1923. Dr. Arthurs was a retired member of the San Francisco Medical Society.

BARBER, CLIFFORD A., Glendale. Died November 9, 1975 in Glendale of heart disease, aged 62. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1942. Licensed in California in 1945. Dr. Barber was a member of the Los Angeles County Medical Association.

BARTLETT, CLIFFORD L., Pasadena. Died June 27, 1975 in Pasadena of pneumonia, aged 85. Graduate of Indiana University School of Medicine, Indianapolis, 1914. Licensed in California in 1928. Dr. Bartlett was a member of the Los Angeles County Medical Association.

BOND, ROBERT EMERSON, San Diego, Died October 31, 1975 in San Diego, aged 73. Graduate of the University of Illinois College of Medicine, Chicago, 1926. Licensed in California in 1926. Dr. Bond was a retired member of the San Diego County Medical Society.

BOWNS, HAROLD CHRISTEN, Folsom. Died October 3, 1975 in Salt Lake City of heart disease, aged 59. Graduate of the University of Southern California School of Medicine, Los Angeles, 1956. Licensed in California in 1957. Dr. Bowns was a member of the Sacramento County Medical Association.

BURNETT, JOHN F., Hoopa. Died November 17, 1975 near Hoopa of injuries received in automobile accident, aged 54. Graduate of the University of Washington School of Medicine, Seattle, 1953. Licensed in California in 1957. Dr. Burnett was a member of the Humboldt-Del Norte County Medical Society.

DANIELS, CHARLES J., Los Angeles. Died October 20, 1975 in Jackson, Wyoming of heart disease, aged 58. Graduate of the University of Southern California School of Medicine, Los Angeles, 1944. Licensed in California in 1944. Dr. Daniels was a member of the Los Angeles County Medical Association.

DE WEESE, ROBERT CORNELL, JR., Los Angeles. Died August 29, 1975 in San Gabriel of heart disease, aged 54. Graduate of the University of Colorado School of Medicine, Denver, 1952. Licensed in California in 1954. Dr. De Weese was a member of the Los Angeles County Medical Association.

EDGERTON, AMBROSE EARL, San Francisco. Died October 15, 1975 in San Francisco, aged 86. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1914. Licensed in California in 1915. Dr. Edgerton was a retired member of the San Francisco Medical Society.

EDWARDS, HAROLD THEODORE, Los Molinos. Died October 14, 1975 in Corning of heart disease, aged 65. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1935. Licensed in California in 1935. MD degree from California College of Medicine, 1962. Dr. Edwards was a member of the 41st Medical Society.

FRIEDLANDER, ERNST, San Jose. Died June 18, 1975, aged 85. Graduate of Medizinische Fakultät der Universität, Wien, 1907. Licensed in California in 1941. Dr. Friedlander was a retired member of the Santa Clara County Medical Society.

GILKEY, WALTER DONALD, Long Beach. Died October 6, 1975 in London, aged 80. Graduate of Western Reserve University School of Medicine, Cleveland, 1921. Licensed in California in 1929. Dr. Gilkey was a member of the Los Angeles County Medical Association.

GRIFFITH, GEORGE CUPP, Los Angeles. Died October 26, 1975 in Los Angeles of heart disease, aged 77. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1926. Licensed in California in 1946. Dr. Griffith was a member of the Los Angeles County Medical Association.

HAND, LEE JAMES, San Francisco. Died October 2, 1975 in Walnut Creek, aged 75. Graduate of the Creighton University School of Medicine, Omaha, 1926. Licensed in California in 1929. Dr. Hand was a member of the San Francisco Medical Society.

HARTLEY, PHILIP B., Long Beach. Died October 26, 1975 in Long Beach of carcinomatosis, aged 55. Graduate of the University of Southern California School of Medicine, Los Angeles, 1945. Licensed in California in 1945. Dr. Hartley was a member of the Los Angeles County Medical Association.

HAYES, EDWARD WILLIAM, Monrovia. Died October 2, 1975 in Duarte of cerebrovascular accident, aged 92. Graduate of the University of Minnesota Medical School, Minneapolis, 1913. Licensed in California in 1919. Dr. Hayes was a retired member of the Los Angeles County Medical Association.

LEEF, EDWARD, Fresno. Died October 5, 1975 in Fresno, aged 78. Graduate of the University of Minnesota Medical School, Minneapolis, 1927. Licensed in California in 1931. Dr. Leef was a member of the Fresno County Medical Society.

LINSEY, RALPH MORRIS, San Jose. Died June 17, 1975, aged 56. Graduate of Hahnemann Medical College and Hospital of Philadelphia, 1945. Licensed in California in 1950. Dr. Linsey was a member of the Santa Clara County Medical Society.

LITWINENCO, JOHN I., Pomona. Died July 4, 1975 in Upland of cerebrovascular accident, aged 78. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1935. Licensed in California in 1935. Dr. Litwinenco was a member of the Los Angeles County Medical Association.

MURPHY, CHARLES F., Pasadena. Died October 30, 1975 in Pasadena, aged 67. Graduate of St. Louis University School of Medicine, 1934. Licensed in California in 1937. Dr. Murphy was a member of the Los Angeles County Medical Association.

PIPER, WILLIAM NELSON, Pacific Palisades. Died September 3, 1975 of cancer of the lung in Santa Monica, aged 62. Graduate of the University of Illinois College of Medicine, Chicago, 1939. Licensed in California in 1954. Dr. Piper was a member of the Los Angeles County Medical Association.

PLIMPTON, EDWIN, Los Angeles. Died August 21, 1975 in Los Angeles of heart disease, aged 75. Graduate of State University of Iowa College of Medicine, Iowa City, 1926. Licensed in California in 1928. Dr. Plimpton was a member of the Los Angeles County Medical Association.

RABINOWITZ, RALPH, San Francisco. Died October 16, 1975, aged 81. Graduate of the University of California Medical School, Berkeley-San Francisco, 1918. Licensed in California in 1918. Dr. Rabinowitz was a member of the San Francisco Medical Society.

SLOANE, GERALD LEROY, Beverly Hills. Died July 30, 1975 in Los Angeles of carcinoma of the colon and heart disease, aged 49. Graduate of McGill University Faculty of Medicine, Montreal, 1953. Licensed in California in 1954.

STAUB, JOHN GARFIELD, JR., Claremont. Died October 4, 1975 in Pomona, aged 68. Graduate of Washington University School of Medicine, St. Louis, 1932. Licensed in California in 1932. Dr. Staub was a member of the Los Angeles County Medical Association.

SUGARMAN, JEROME N., Los Angeles. Died October 19, 1975 in Los Angeles of myocardial infarction, aged 60. Graduate of the University of Southern California School of Medicine, Los Angeles, 1941. Licensed in California in 1941. Dr. Sugarman was a member of the Los Angeles County Medical Association.

THOMPSON, HAROLD L., Los Angeles. Died August 28, 1975 in Glendale of cancer of the prostate, aged 78. Graduate of Rush Medical School, Chicago, 1924. Licensed in California in 1924. Dr. Thompson was a member of the Los Angeles County Medical Association.

TILLEY, CHARLES RAY, Oxnard. Died November 1, 1975 in Santa Barbara, aged 72. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1930. Licensed in California in 1930. MD degree from California College of Medicine, 1962. Dr. Tilley was a member of the Ventura County Medical Society.

WASLEY, MALCOLM TUCKER, Whittier. Died November 24, 1975 of heart disease, aged 59. Graduate of Hahnemann Medical College and Hospital of Philadelphia, 1943. Licensed in California in 1948. Dr. Wasley was a member of the Los Angeles County Medical Association.

WATENMAKER, HERMAN B., Los Angeles. Died July 27, 1975 in Los Angeles of primary amyloidosis, aged 58. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1941. Licensed in California in 1941. MD degree from California College of Medicine, 1962. Dr. Watenmaker was a member of the Los Angeles County Medical Association.

WEISS, MAURICE RICHARD, Los Angeles. Died November 11, 1975 in Beverly Hills of cancer, aged 59. Graduate of the University of Maryland School of Medicine, Baltimore, 1943. Licensed in California in 1946. Dr. Weiss was a member of the Los Angeles County Medical Association.

PROPOSED CMA CONSTITUTIONAL AMENDMENTS

FOR ACTION IN 1976

Three Constitutional amendments were introduced in the 1975 House of Delegates. Under the terms of the Constitution, these amendments must lie on the table until the next regular meeting of the House of Delegates.

The proposed amendments are shown here for the information of the membership. In addition, the proposed Constitutional amendments are required to be printed in two issues of *The Western Journal of Medicine* before they come before the House of Delegates for action.

CMA CONSTITUTIONAL AMENDMENT PERMITTING VOLUNTARY MEMBERSHIP IN CMA AND AMA BY A MEMBER OF A COMPONENT COUNTY MEDICAL ASSOCIATION

Introduced by: LACMA Delegation
Representing: Los Angeles County
Author: Allan K. Briney, MD

Constitutional Amendment No. 1-75
Committee G

Whereas, the present Bylaws of the California Medical Association make membership in the California Medical Association and the American Medical Association compulsory to all members of a component county medical society; and

Whereas, we, as a profession, vigorously defend the principle of "freedom of choice" in health care, yet deny individual members of county medical societies the freedom of deciding whether or not they wish to belong to the California Medical Association or American Medical Association; and

Whereas, each physician is quite capable of deciding whether there are sufficient advantages or insufficient advantages to maintaining membership in all three organizations; and

Whereas, mandatory membership in one organization (CMA and AMA) in order to maintain membership in another (local medical society) significantly interferes with the privileges of setting priorities as to organizational commitments, such as belonging to specialty societies; and

Whereas, in at least forty states a local county medical association member may decide for himself whether he also wishes to maintain membership in the state and national medical associations; e.g., New York and Massachusetts; and

Whereas, professional liability insurance carriers have no requirements about California Medical Association or American Medical Association membership for coverage of a county medical society member; and

Whereas, in a free and democratic society it would seem reasonable and consistent that membership in all medical societies should be voluntary, with each society attracting members on its own merits; and

Whereas, there is widespread feeling among local county medical association members that the CMA and AMA have long ago lost their "grass roots" contact and cannot speak authoritatively for the medical profession; now, therefore, be it

Resolved: That Article I, Section 3, be amended as follows:

This Association is an organization composed of the component societies and their members who are members of this Association, the House of Delegates, the Council, the Scientific Board, the Scientific Assembly, Bureaus, Commissions and Standing Committees.

ACTION: Tabled for one year; to be acted upon at the 1976 meeting of the House of Delegates.

* * *

SCIENTIFIC BOARD DELEGATES

Introduced by: ad hoc Committee on the Study of the Election Process of the Scientific Board
Representing: ad hoc Committee on the Study of the Election Process of the Scientific Board
Author: Frederick S. Armstrong, MD

Constitutional Amendment No. 2-75
Committee G

Resolved: That Article III, Part A, Section 1-d of the California Medical Association Constitution and Bylaws shall be amended by deleting the words in brackets and substituting the words in italics so that this Section shall read:

(d) [Ex-officio, without the right to vote, eighteen (18) members of the Scientific Board selected as provided in the Bylaws.] *Delegates elected by the Scientific Board.*

ACTION: Tabled for one year; to be acted upon at the 1976 meeting of the House of Delegates.

* * *

ARTICLE I, SECTION 2: NAME, PURPOSES AND ORGANIZATION

Introduced by: Henry S. Richanbach, MD
Author: William Rosenzweig, MD

Constitutional Amendment No. 3-75
Committee G

Whereas, the right of each individual to associate, or not associate freely with legally constituted organizations may not be abridged by virtue of our Constitutional rights; and

Whereas, the California Medical Association, by virtue of its mandatory requirement that the individual members and member associations affiliate themselves with the American Medical Association, it is patently clear that these rights have been, and are being abridged; now, therefore, be it

Resolved: That Article I, Section 2 of the Constitution be amended as follows:

The purposes of this Association are to promote the science and art of medicine, the protection of public health, and the betterment of the medical profession; to promote similar interests of its component societies.

ACTION: Tabled for one year; to be acted upon at the 1976 meeting of the House of Delegates.

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Prophylactically, the ointment may be used to prevent bacterial contamination in burns, skin grafts, incisions, and other clean lesions. For abrasions, minor cuts and wounds accidentally incurred, its use may prevent the development of infection and permit wound healing. **CONTRAINDICATIONS:** Not for use in the eyes or external ear canal if the eardrum is perforated. This product is contraindicated in those individuals who have shown hypersensitivity to any of the components. **WARNING:** Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended. **PRECAUTIONS:** As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs. **ADVERSE REACTIONS:** Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

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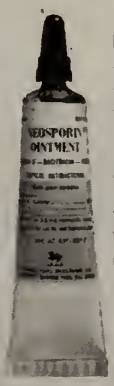

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(Continued from Page 6)

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PULMONARY INTERNIST WANTED to join pulmonary group practice in San Diego, California. Practice includes office care, hospital consultations, and medical direction of Respiratory Therapy-Pulmonary Function Departments. Reply with curriculum vitae to: Jerry E. Fein, MD, Pulmonary Associates Medical Group, Inc., 6355 Ridge Manor Ave., San Diego, CA 92120; (714) 462-3360.

CALIFORNIA—CHIEF OF UROLOGY. University-affiliated hospital in delightful California city is seeking an academically oriented urologist to head Department of Urology. Full-time or geographic full-time. Professional liability insurance paid. Equal Opporunity Employer. Send curriculum vitae in first letter to: Jerome S. Harris, MD, Director of Medical Affairs, Valley Medical Center of Fresno, 445 So. Cedar, Fresno, CA 93702.

CALIFORNIA—CHIEF OF OPHTHALMOLOGY. University-affiliated hospital in delightful California city is seeking an academically oriented ophthalmologst to head Department of Ophthalmology. Half-time. Professional liability insurance paid. Equal Opportunity Employer. Send curriculum vitae in first letter to: Jerome S. Harris, MD, Director of Medical Affairs, Valley Medical Center of Fresno, 445 So. Cedar, Fresno, CA 93702.

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BOARD ELIGIBLE, OB/GYN, married, 31, University trained, experienced in laparoscopy, fetal monitoring, pregnancy termination, infertilty. Seeks affiliation with grcup of three or more. Military completed and available July 1976. Write Box No. 9456, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

BOARD CERTIFIED INTERNIST. Insurance medicine background. Seeks position in San Francisco area. Write Box No. 9458, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: For a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education, please write to the above address.

CANCER

January 16-17—**Childhood Cancer: Major Clinical Advances and New Problems in Family Adjustment.** Children's Hospital of L.A. and American Cancer Society at Children's Hospital, Los Angeles. Friday-Saturday. Contact: Daniel M. Hays, MD, Children's Hospital, P.O. Box 54700, Los Angeles 90054. (213) 660-2450, ext. 2675.

January 16-18—**Gynecologic Oncology.** Women's Hospital Medical Center at Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Sunday. 15 hrs. $200; $100, residents. Contact: Margaret Frederick, Exec. Sec., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

January 19-23—**Cancer.** STAN. Monday-Friday.

January 28—**Lung Cancer.** Hospital of the Good Samaritan, Los Angeles. Wednesday. Contact: Janie Sternal, Coord., CME, Hospital of the Good Samaritan, 1212 Shatto St., Los Angeles 90017. (213) 482-8111.

February 27—**Breast Cancer.** UCSF at Childrens Hospital and Medical Center, San Francisco. Friday.

February 27—**Current Cancer Therapy Concepts and the Animal Patient Role.** Kern County Unit, American Cancer Society. Friday. 8 hrs. $25. Contact: Elizabeth Bell, Exec. Dir., Kern County Unit, ACS, 238 18th St., Suite 10, Bakersfield 93301. (805) 325-5117.

March 4-7—**Seminar on Modern Concepts in Oncology—4th Annual.** UCLA at Beverly Hilton Hotel, Beverly Hills. Thursday-Sunday.

March 25-26—**Clinical Cancer Conference—11th Annual.** UCSF at St. Francis Hotel, San Francisco. Thursday-Friday.

March 26—**Colo-Rectal Carcinoma.** California Hospital Medical Center, Los Angeles. Friday. 10 hrs. $15. Contact: Kenneth L. Senter, MD, Dir., Med. Ed., CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411.

April 3—**Oncology Update 1976.** Alta Bates Hospital, Berkeley. Saturday. 8 hrs. $20. Contact: Norman Cohen, MD or Harry Newman, MD, Alta Bates Hospital, No. 1 Colby Plaza, Berkeley 94705. (415) 845-7110.

MEDICINE

January 16—**Current Concepts in Management of Thyroid Disorders.** Cedars-Sinai Medical Center at Mt. Sinai Hospital, Los Angeles. Friday. Contact: Linda Alperstein, Coord., CME, Cedars-Sinai Medical Center, 4833 Fountain Ave., Los Angeles 90029. (213) 662-9111, ext. 206.

January 16-18—**Third Neonatal Respiratory Symposium.** See Surgery and Anesthesiology, January 16-18.

January 20-23—**Internal Medicines and the Practice of Internal Medicine: 1976.** American College of Physicians at Letterman Army Medical Center, San Francisco. Tuesday-Friday. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104 or Milton K. McDowell, MD, Col., MC, Asst. Chief, Dept. of Medicine, Letterman Army Medical Ctr., Presidio of San Francisco 94129.

February 5-6—**Contact Dermatitis.** STAN. Thursday-Friday.

February 14—**Annual Cardiology Symposium.** Fresno Community Hospital. Saturday. Contact: Joanne Ellis, Fresno Community Hospital, P.O. Box 1232, Fresno 93715.

February 16-20—**Topics in Internal Medicine. UCSD** at Town and Country Hotel, San Diego. Monday-Friday.

February 25-27—**Advances in the Diagnosis and Treatment of Pulmonary Disease.** California Thoracic Society at Sheraton-Harbor Island Hotel, San Diego. Wednesday-Friday. 20 hrs. $135 for members; $160, non-members. Contact: Ms. Elma

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

Plappert, Exec. Sec., CTS, 424 Pendleton Way, Oakland 94621. (415) 638-5864.

February 26-27—**Dermatologic Therapy for the Practicing Physician.** UCSF at St. Francis Hotel, San Francisco. Thursday-Friday.

February 26-28—**Pediatric Hematology.** See Pediatrics, February 26-28.

February 27-28—**Pulmonary Artery Catheterization.** PMC. Fri.-Sat.

March 1-5—**Electrophysiology.** USC at Erawan Garden Hotel, Palm Springs. Monday-Friday.

March 4-5—**Diabetes.** USC at Good Samaritan Hospital, Los Angeles. Thursday-Friday.

March 4-6—**Cardiology '76—Practical Aspects of Cardiac Care.** American Heart Assn.-Golden Empire Chapter at Sahara Tahoe Hotel, Lake Tahoe. Thursday-Saturday. Contact: AHA-Golden Empire Chapter, P.O. Box 16011, Sacramento 95816. (916) 444-8650.

March 4-7—**American College of Physicians-Southern California Regional Meeting.** Riviera Hotel, Palm Springs. Thursday-Sunday. Contact: Varner J. Johns, Jr., MD, FACP, Loma Linda Medical Center, Loma Linda 92354.

March 5—**Diabetes—3rd Annual Program.** UCD at Red Lion Inn, Sacramento. Friday.

March 6—**Echocardiography Workshop.** PMC. Saturday.

March 11-13—**Cardiovascular Disease—1976: Practical Diagnosis and Management.** American College of Cardiology at La Costa Resort Hotel, San Diego. Thursday-Saturday. Contact: ACC, 9650 Rockville Pike, Bethesda, MD 20014.

March 12—**Diagnosis and Treatment of Hypertension.** PMC. Friday.

March 20-21—**Theory and Practice of Echocardiography.** UCLA. Saturday-Sunday.

March 22-April 2—**Intensive Review of Internal Medicine.** USC. Two weeks.

March 26-27—**New Perspectives in Exercise Stress Testing.** American College of Cardiology; Memorial Hospital Medical Center, Long Beach; UCI at Center for Health Education, Memorial Hospital, Long Beach. Friday-Saturday. Contact: ACC, 9650 Rockville Pike, Bethesda, MD 20014.

March 30-April 2—**Consultant's Course in Dermatology.** UCSF. Tuesday-Friday.

April 1-2—**Core Curriculum: Cardiovascular Physiology: Clinical Implications of Newer Concepts and Measurements.** American College of Cardiology at Cedars-Sinai Medical Center, Los Angeles. Thursday-Friday. Contact: ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

April 1-3—**Advances in Cardiology.** Foundation for Cardiovascular Research and Hospital of the Good Samaritan at Balboa Bay Club, Newport Beach. Thursday-Saturday. Contact: Foundation for Cardiovascular Research, 39 Congress St., Pasadena 91105.

April 5-14—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe. 10 days. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

April 7-9—**Hepato-Billiary Disease.** PMC. Wednesday-Friday.

April 11-16—**American Association of Immunologists.** Royal Hotel, Anaheim. Sunday-Friday. Contact: H. Metzger, MD, Sec.-Treas., AAI, 9650 Rockville Pike, Bethesda, Md. 20014.

April 30—**Flexible Bronchofibroscopy II.** PMC. Friday.

OBSTETRICS AND GYNECOLOGY

January 16-18—**Third Neonatal Respiratory Symposium.** See Surgery and Anesthesiology, January 16-18.

January 16-19—**Basic Laparoscopy: Current Principles and Practice.** UCSD at Sea Lodge, La Jolla. Friday-Monday.

January 17-24—**Perinatal Medicine.** USC at Royal Lahaina, Maui, Hawaii. One week.

February 7-8—**Obstetrical and Gynecological Forum.** Los Angeles Obstetrical & Gynecological Society at Beverly Hilton Hotel, Los Angeles. Saturday-Sunday. 14 hrs. $45. Contact: Miss Dee Davis, Exec. Sec., L.A. Ob & Gyn Society, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

February 9-11—**Workshop in Perinatal Infections.** Kapiolani Hospital, Honolulu, Hawaii. Monday-Wednesday. $100. Contact: Wilma B. Schiner, RN, Dir. of Training & Education, Kapiolani Hospital, 1319 Punahou St., Honolulu 96814.

February 18-20—**Neonatal Medicine.** USC. Wednesday-Friday.

February 24-26—**Ob Infectious Diseases.** USC. Tuesday-Thursday.

March 5-7—**Obstetric Anesthesia Conference—Part I.** L.A. Obstetrical & Gynecological Society at Sheraton Airport Hotel, Los Angeles. Friday-Sunday. Contact: Perinatal

1976 Winter Conference Schedule

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FEBRUARY 14-21
Vail Ob-Gyn Conference

FEBRUARY 21-28
Vail Family/General Practice Conference

FEBRUARY 28-MARCH 6
Aspen Radiology Conference

MARCH 6-13
Aspen Psychiatry Conference

MARCH 13-20
Vail General Surgery Conference

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March 8-11—**Obstetric Anesthesia Conference—Part II.** L.A. Obstetrical and Gynecological Society at Sheraton-Maui Hotel, Maui, Hawaii. Monday-Thursday. Contact: Perinatal Anesthesia, P.O. Box 54508, Los Angeles 90054. (213) 226-3311.

March 13—**Regional Perinatal Care Conference.** CMA at Hollywood Presbyterian Hospital, Hollywood. Saturday. Contact: George Feiler, CMA.

PEDIATRICS

January 23-25—**Pediatric Anesthesiology.** See Surgery and Anesthesiology, January 23-25.

January 24-25—**Down's Syndrome.** UCLA. Saturday-Sunday.

February 12—**Psycho-Social Aspects of Orofacial Clefts—4th Annual Cleft Palate Seminar.** See Of Interest To All, February 12.

February 18—**The Pediatrician's Obligation in the Atherosclerosis Epidemic.** American Heart Assn., Greater L.A. Affiliate, and L.A. Pediatric Society at Hyatt Regency Hotel, Los Angeles. Wednesday. Contact: Nancy Brown, AHA, Greater L.A. Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

February 21—**The Teenager's Doctor—A Key to Understanding Youth.** American Academy of Pediatrics, No. Calif. Chapter, at Children's Hospital, San Francisco. Saturday. 6 hrs. $25. Contact: Richard C. Brown, MD, Dept. of Pediatrics, Children's Hospital, 3700 California St., San Francisco 94119. (415) 387-8700.

February 26-28—**Pediatric Hematology—Annual Winter Meeting.** Children's Hospital Medical Center of Northern Calif. at Sahara Tahoe Hotel, South Lake Tahoe. Thursday-Saturday. Contact: Inetta Carty Calori, CHMC, 51st & Grove Sts., Oakland 94609.

March 19-21—**Combined Southern California Pediatric Postgraduate Meeting: Clinical Pediatrics.** Calif. Chapter 2, District IX, American Academy of Pediatrics, at Riviera Hotel, Palm Springs. Friday-Sunday. Contact: Eve Black, Exec. Sec., P.O. Box 2134, Inglewood 90305.

March 26-27—**Pediatric Topics 1976: Neonatology and Pediatric Cardiology.** UCD and Sacramento Pediatric Society at Mansion Inn, Sacramento. Friday-Saturday. Contact: UCD.

April 23-24—**Pediatric Ophthalmology.** See Surgery, April 23-24.

April 24-May 1—**Pediatric Review.** USC at Maui Surf, Hawaii. One week.

PSYCHIATRY

January-April—**Intensive Review Course: American Board of Psychiatry and Neurology.** UCD at South Area Mental Health Center, Sacramento. Tuesdays, 7-10 p.m. 41 hrs.

January 7-March 17—**Intensive Review of Psychiatry and Neurology.** USC. Wednesdays, 10:00 a.m.-12:00 noon.

February 1-6—**Psychiatry Update: 2nd Annual Mid-Winter Program for Psychiatrists.** UCD at Bear Valley. Sunday-Friday.

February 16-20—**Treating Distressed Couples: The Masters and Johnson Method.** Center for Counseling Skills, Kentfield, at Santa Barbara. Monday-Friday. Contact: Mrs. Tina Coffman, Extension Office, UCSB, Santa Barbara 93106.

February 21-22—**Introduction to Clinical Hypnosis and Behavior Modification.** UCLA at Americana Hotel, Los Angeles. Saturday-Sunday.

February 21-22—**Psychiatric Techniques in the Treatment of Drug Abuse and Alcoholism.** UCLA. Saturday-Sunday.

February 27-29—**Current Therapy for Marital-Sexual Dysfunction.** The Center for Counseling Skills, Kentfield, at Palo Alto. Friday-Sunday. Contact: Center for Creativity and Growth, Suite 154, 770 Welch Rd., Palo Alto 94304. (415) 327-4477.

March 5-7—**Current Therapy for Marital-Sexual Dysfunction.** Center for Counseling Skills, Kentfield, at Palo Alto. Friday-Sunday. Contact: Center for Creativity and Growth, Suite 154, 770 Welch Rd., Palo Alto 94304. (415) 327-4477.

March 13-14—**Advanced Workshop in Hypnosis and Behavior Modification.** UCLA at Marina City Club, Marina Del Rey. Saturday-Sunday.

March 18—**The Compromised Psychophysiologic State or "Why Can't You Make Me Well?"** See Of Interest To All, March 18.

April 3-4—**Hypnosis for the Treatment for Sexual Dysfunction.** UCLA. Saturday-Sunday.

April 11-14—**Psychiatric Update.** UCLA at Riviera Hotel, Palm Springs. Sunday-Wednesday.

RADIOLOGY AND PATHOLOGY

January-May—**Ultrasound — Comprehensive Lecture Series.** USC. Weekly, 7:00-9:00 p.m., 20 consecutive weeks. Contact: Robert L. Wilson, MD, P.O. Box 1961, 1200 N. State St., Los Angeles 90033.

January 30-February 1—**Midwinter Radiological Conference—28th Annual.** L.A. Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Los Angeles Radiological Society, 15107 Vanowen St., Van Nuys 91405.

February 5-6—**Paternity Testing: Present and Future.** Memorial Hospital Medical Center and American Society of Clinical Pathologists at MHMC-UCI Center for Health Education, Long Beach. Thursday-Friday. $125. Contact: Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

February 14—**The Pathology of Fatal Liver Disease.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. $85. Contact: Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

March 13-14—**Diagnostic Nuclear Imaging.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

March 15-19—**Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday.

March 20-21—**Ultra Sound, A Practical Course.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

March 21-25—**Cardiac Radiology Refresher Course.** North American Society for Cardiac Radiology at Sir Francis Drake Hotel, San Francisco. Sunday-Thursday. Contact: Erik Carlsson, MD, Dept. of Radiology, UCSF.

April 11-16—**American Society for Experimental Pathology.** Anaheim. Sunday-Friday. Contact: Am. Soc. for Experimental Pathology, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-7130.

April 24-May 1—**Chest and G.I. Radiology.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week.

SURGERY AND ANESTHESIOLOGY

January-April—**Intensive Review Course: American Board of Psychiatry and Neurology.** See Psychiatry, January-April.

January 7-March 17—**Intensive Review of Psychiatry and Neurology.** See Psychiatry, January 7-March 17.

January 8-9—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

January 9—**Vitreal and Retinal Surgery Workshop.** Jules Stein Eye Institute, Los Angeles. Friday. Contact: Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles.

January 9-10—**Phacoemulsification Conference.** St. Mary's Hospital and Medical Center, San Francisco. Friday-Saturday. Contact: J. Albert Sarrail, MD, 450 Sutter St., San Francisco. (415) 397-1500.

January 10-17—**Super Seminar '76—First Annual Conference on the Foot and Ankle.** California College of Podiatric Medicine at St. Francis Hotel, San Francisco. One week. Contact: Super Seminar, P.O. Box 7855, Rincon Annex, San Francisco 94120.

January 11-17—**Otologic Surgery Course.** Ear Research Institute, Los Angeles. One week. 48 hours. $550; $350 for residents. Contact: F. H. Linthicum, Jr., MD, Dir. of Education, Ear Research Institute, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

January 16-18—**Third Neonatal Respiratory Symposium.** California Society of Anesthesiologists at Marriott Hotel, Los Angeles. Friday-Sunday. Contact: Perinatal Anesthesia, P.O. Box 54508, Los Angeles 90054. (213) 226-3311.

January 17—**Vascular Disease—3rd Annual Symposium.** UCSD at UC Medical Center, San Diego. Saturday.

January 21-23—**Sierra Traumatological Society—5th Annual Meeting.** See Of Interest To All, January 21-23.

January 23-25—**Pediatric Anesthesiology—14th Clinical Conference.** Childrens Hospital of L.A. at Marriott Hotel, Los Angeles. Friday-Sunday. 15 hrs. $100. Contact: Wayne Herbert, MD, CHLA, P.O. Box 54700, Los Angeles 90054. (213) 663-3341, ext. 2262.

January 25-30—**Postgraduate Institute on Emergency Medicine.** See Of Interest To All, January 25-30.

January 26-30—**Topics in Emergency Medicine.** See Of Interest To All, January 26-30.

January 28-30—**Advances in Neurology.** UCSF. Wednesday-Friday.

February 1-4—**Theodor Billroth Course in Surgical Anatomy.** LLU. Sunday-Wednesday.

February 5-6—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

February 6—**Photocoagulation Therapy Workshop.** Jules Stein Eye Institute, Los Angeles. Friday. Contact: Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles.

February 11-13—**Clinical Applications of Vitreous Surgery.** USC. Wednesday-Friday.

February 12-15—**Symposium on Controversial Areas in Surgery of the Head and Neck—5th Annual.** UCSD. Thursday-Sunday. Contact: UCSD or Alan M. Nahum, MD, University Hospital, 225 W. Dickinson, San Diego 92103.

February 13-14—**Phacoemulsification Conference.** St. Mary's Hospital and Medical Center, San Francisco. Friday-Saturday. Contact: J. Albert Sarrail, MD, 450 Sutter St., San Francisco. (415) 397-1500.

March 5—**Strabismus Surgery Workshop.** Jules Stein Eye Institute, Los Angeles. Friday. Contact: Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles.

March 5-7—**Obstetric Anesthesia Conference, Part I.** See Obstetrics and Gynecology, March 5-7.

March 6-7—**American Society of Anesthesiologists Workshop.** Sheraton-Harbor Island Hotel, San Diego. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, Ill. 60068.

March 8-11—**Obstetric Anesthesia Conference, Part II.** See Obstetrics and Gynecology, March 8-11.

March 9-13—**Seminar on Controversial Areas in Surgery—13th Annual.** UCLA at Canyon Hotel, Palm Springs. Tuesday-Saturday.

March 11-12—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

March 12-13—**Hand Injuries and Infections.** PMC. Friday-Saturday.

March 13-17—**Multidiscipline Symposium and Workshop on Management of Trauma—3rd Annual.** UCLA at Canyon Hotel, Palm Springs. Saturday-Wednesday.

March 14-26—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. 100 hrs. $1,200 for otolaryngologists; $900, residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

March 17-21—**Symposium on Vascular Surgery—4th Annual.** UCLA at Canyon Hotel, Palm Springs. Wednesday-Sunday.

March 18-19—**Diseases of the Urinary Tract—4th Annual Symposium.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday.

March 22-26—**Anesthesiology—1976.** Anesthesiology Education Foundation and Calif. Society of Anesthesiologists at Mammoth Lakes. Monday-Friday. Contact: Ronald L. Katz, MD, Dept. of Anesthesiology, UCLA.

March 22-26—**Trauma and Surgical Emergencies.** STAN. Monday-Friday.

March 27-29—**Developmental and Acquired Jaw Problems.** UCLA. Saturday-Monday.

April 2—**Corneal Surgery Workshop.** Jules Stein Eye Institute, Los Angeles. Friday. Contact: Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles.

April 7-10—**California Thoracic Society—Annual Scientific Sessions.** Rickey's Hyatt House, Palo Alto. Wednesday-Saturday. Contact: Ms. Elma Plappert, Exec. Sec., CTS, 424 Pendleton Way, Oakland 94621. (415) 638-5864.

April 8-9—**Ophthalmic Skills.** PMC. Thursday-Friday.

April 8-9—**Office Orthopedics.** USC. Thursday-Friday.

April 9-10—**Phacoemulsification Conference.** St. Mary's Hospital and Medical Center, San Francisco. Friday-Saturday. Contact: J. Albert Sarrai, MD, 450 Sutter St., San Francisco. (415) 397-1500.

April 22-23—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

April 22-24—**General Surgery—Annual Course.** UCSF at Hilton Hotel, San Francisco. Thursday-Saturday.

April 23-24—**Pediatric Ophthalmology—A Current Review—7th Annual Jules Stein Lecture and Postgraduate Seminar.** Jules Stein Eye Institute at Beverly Hilton Hotel, Los Angeles. Friday-Saturday. Contact: Jules Stein Eye Institute, UCLA.

April 23-25—**American Association for Thoracic Surgery.** Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Mr. W. T. Maloney, Exec. Sec., 6 Beacon St., Suite 620, Boston, Mass. 02108. (617) 227-0760.

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OF INTEREST TO ALL PHYSICIANS

January 21—**Hospital Infection Control: "Spirit of '76."** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday. $20. Contact: Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

January 21-23—**Sierra Traumatological Society—5th Annual Meeting.** Kirkwood Meadows. Wednesday-Friday. Contact: William E. Latham, MD, Sierra Traumatological Society, P.O. Box 230, Stockton 95201. (209) 466-9535.

January 21-24—**The Physician and the Hospital.** USC at Canyon Hotel, Palm Springs. Wednesday-Saturday.

January 23-24—**Management of Stress in the Middle Years.** Vista Hill Foundation at Hilton Inn, San Diego. Friday-Saturday. Contact: Virginia Everett, Dir., Public Relations, Vista Hill Foundation, 7798 Starling Dr., San Diego 92123.

January 24-25—**Ways of Healing: Ancient and Modern.** Institute for the Study of Human Knowledge and UCSF at Sheraton-Palace Hotel, San Francisco. Saturday-Sunday. Contact: Ms. Mae Ling Yee, Cont. Ed. in Health Sciences, C135G, UCSF. (415) 666-2894.

January 25-30—**Postgraduate Institute on Emergency Medicine.** UCLA at Beverly Hilton Hotel, Beverly Hills. Sunday-Friday.

January 26-30—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

February 2-7—**Family Practice Review Course—7th Annual.** UCI at Newporter Inn, Newport Beach. Monday-Saturday.

February 6-11—**California Medical Association—105th Annual Session.** Hyatt Regency Hotel, San Francisco. Friday-Wednesday.

February 7—**The Practical Applications of Biofeedback in Medicine.** Department of Physical Medicine & Rehabilitation, Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 6 hrs. $75. Contact: Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

February 10-14—**Autogenics Training Techniques Workshop.** UCLA at Lake Arrowhead. Tuesday-Saturday.

February 11-13—**Ambulatory Health Care Symposium.** Naval Regional Medical Center, San Diego; UCSD at Hilton Inn, Mission Bay, San Diego. Wednesday-Friday. Contact: CAPT. Joseph D. Bloom, MC, USN, Chr., Dept. of Int. Med., Naval Regional Medical Center, San Diego 92134.

February 11-13—**Course for Physicians in Family Practice—26th Annual.** Mt. Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. $110. Contact: Dept. of Continuing Education, Mt. Zion Hospital, 2511 Bush St., San Francisco 94115. (415) 567-6600, ext. 2401.

February 12—**Psycho-Social Aspects of Orofacial Clefts—4th Annual Cleft Palate Seminar.** Cleft Palate Team, Rancho Los Amigos Hospital; USC; L.A. County Nat'l Foundation March of Dimes at Rancho Los Amigos Hospital, Downey. Wednesday. Contact: Cleft Palate Service, Rancho Los Amigos Hosp., 7601 E. Imperial Highway, Downey 90242. (213) 922-7454.

February 13-14—**Diving Medicine for Practicing Physicians.** UCSF at Holiday Inn-Union Square, San Francisco. Friday-Saturday.

February 15-19—**Sports Medicine for Primary Physicians.** Univ. of Hawaii School of Medicine at North Shore of Oahu, Hawaii. $200. Sunday-Thursday. Contact: Richard H. Strauss, MD, Univ. of Hawaii Conference Ctr., 2500 Dole St., Honolulu 96822.

February 16-20—**Treating Distressed Couples: The Masters and Johnson Method.** See Psychiatry, February 16-20.

February 20—**Total Parenteral Nutrition Workshop.** UCD at Red Lion Inn, Sacramento. Friday.

February 27-29—**Current Therapy for Marital-Sexual Dysfunction.** See Psychiatry, February 27-29.

February 28-29—**Infectious Disease and Pulmonary Disease for Family Practitioners.** UCLA. Saturday-Sunday.

March 1-5—**Basic Science for Clinicians.** STAN. Monday-Friday.

March 5-7—**Current Therapy for Marital-Sexual Dysfunction.** See Psychiatry, March 5-7.

March 7-11—**LLU Alumni Postgraduate Convention.** Sunday-Thursday.

March 7-12—**Emergency Medical Care Review—Part II.** UCD at Hyatt Lake Tahoe Hotel, Incline Village. Sunday-Friday.

March 12—**Diagnosis and Treatment of Hypertension.** See Medicine, March 12.

March 13-17—**Multidiscipline Symposium and Workshop on Management of Trauma.** See Surgery, March 13-17.

March 18—**The Compromised Psychophysiologic State or "Why Can't You Make Me Well?"** Eden Hospital at Willow Park Country Club, Castro Valley. Thursday. 7 hrs. $35. Contact: Ms. Eleanor Sample, Eden Hospital, 20103 Lake Chabot Rd., Castro Valley. (415) 537-1234, ext. 211.

March 19—**Office Management of Parkinsonism.** PMC at Miyako Hotel, San Francisco. Friday.

March 21-23—**Sports Injury Clinic.** CMA, Medical Education Foundation of Santa Barbara County and UCLA at Lakeland Village, Lake Tahoe. Sunday-Tuesday. Contact: Richard Manley, CMA.

March 22-26—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday.

March 26-27—**Use of Ventilators.** PMC. Friday-Saturday.

March 29-April 2—**Basic and Applied Pharmacology.** STAN. Monday-Friday.

April 1-2—**Intensive Care of Critically Ill Patients.** UCSF. Thursday-Friday.

April 5-9—**Diving Medicine.** UCSF at VA Hospital, Fresno. Monday-Friday.

April 8-10—**Otolaryngology for the GP.** UCSF. Thursday-Saturday.

April 23-24—**West Coast Counties Postgraduate Institute.** CMA at Quail Lodge, Carmel Valley. 14 hrs. $60 for CMA members; $90, non-members. Friday-Saturday. Contact: Richard Manley, CMA.

April 26-May 1—**Emergency Medicine.** USC at Kauai Surf, Kauai, Hawaii. Monday-Saturday.

April 26-May 1—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Saturday.

April 29-May 1—**Rehabilitation Medicine.** USC. Thursday-Saturday.

April 29-May 1—**Psychosocial Care of Dying Patient—Doctor:Patient Relationship.** UCSF at St. Francis Hotel, San Francisco. Thursday-Saturday.

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PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Family Practice Center, 3181 S.W. Sam Jackson Park Road, Portland 97201:

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School.

FAMILY PRACTICE

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Family Practice Center, University of Oregon Medical School, Portland. Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

February 16-20—**Seventh Annual General and Family Practice Review.** Sheraton Motor Inn, Portland. Contact: William Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 S.W. Sam Jackson Park Road, Portland, OR 97201.

INTERNAL MEDICINE

May 20-22—**Oregon Society of Internal Medicine Annual Meeting.** Sunriver Lodge, Sunriver, Oregon. Contact: Donald R. Olson, MD, Oregon Society of Internal Medicine, 2164 S.W. Park Place, Portland 97205.

SURGERY

April 2-3—**American College of Foot Surgeons, Western Division.** Portland Hilton Hotel, Portland. Contact: Robert L. Rutherford, D.P.M., 400 - 40th Street, Oakland, California 94609

WASHINGTON, MONTANA, ALASKA and IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

January 16—**Continuing Education Course in Pulmonary Disease.** Friday. Mount Vernon Town and Country Motor Inn, Mount Vernon, WA. 6 hrs. $10. Contact: Dave Chivers, Washington Lung Association, 216 Broadway East, Seattle 98112. (206) 329-4411.

January 22-23—**Pediatric Allergy and Immunology.** Thursday-Friday. Univ. of Wash., Child Development and Mental Retardation Center, Seattle. Hours and fees to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

January 27-30—**Medical-Ski Conference.** Tuesday-Friday. Big Mountain, MT. Contact: R. D. Buchanan, MD, P.O. Box 220, Columbia Falls, MT 59912.

January 30-31—**Tax, Estate and Financial Planning for Physicians.** Friday-Saturday. Olympic Hotel, Seattle. Limited to 50 physicians and spouses. 12 hrs. $75. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. School of Med., Seattle 98195. (206) 543-1050.

February 5-7—**Stroke Symposium.** Thursday-Saturday. Washington Plaza Hotel, Seattle. 12 hrs. Physicians, $40; others, $25. Contact: Northwest Hospital, 1551 North 120th, Seattle 98133. (206) EM 4-0500.

February 6-12—**Critical Care: Maternal and Perinatal.** Friday-Thursday. Sun Valley, Idaho. 21 hrs. MDs, PhDs, $100; others, $75. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

February 12-13—**14th Annual Symposium on Respiratory Disease.** Friday-Saturday. Olympic Hotel, Seattle. 14 hrs. $15. Contact: Ms. Jo Senters, Washington Lung Association, 216 Broadway East, Seattle 98102. (206) 322-7110.

February 18-19—**Treating the Untreatable—Univ. of Washington School of Medicine's Western Washington Circuit Course.** Longview, 18; Olympia, 19. 4 hrs. Physicians, $25; others, $10. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch. of Med., Seattle 98195 (206) 543-1050.

March 4-6—**Symposium on Cancer: Concepts, Care and Ethics.** Swedish Hospital Medical Center, Seattle. Limited to 200. $15. Contact: Office of Medical Education, The Swedish Hospital Medical Center, 747 Summit Ave., Seattle 98104. (206) 292-2266.

March 5-6—**Recent Advances in Renal Disease—27th Annual Spokane Society of Internal Medicine Scientific Session.** Friday-Saturday. Sheraton Hotel, Spokane, WA. AAFP credit approved. Contact: Thomas A. Marr, MD, 312 W. 8th, Spokane, WA 99204. (509) 838-2531.

March 9-10—**Treating the Untreatable—Univ. of Washington School of Medicine's Western Washington Circuit Course.** Port Angeles, 9; Everett, 10. 4 hrs. Physicians, $25; others, $10. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 12-13—**Orthopedic Disease: A Practical Approach to Clinical Management.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

March 15-19—**Emergency Medicine Institute.** Monday-Friday. Univ. of Wash. Sch. of Med., Seattle. 38 hrs. $275. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 18-19—**American Society of Clinical Pharmacology and Therapeutics.** Thursday-Friday. Washington Plaza Hotel, Seattle. Contact: E. H. Funk, MD, 1718 Gallagher Rd., Norristown, PA 19401. (215) 277-3831.

March 18-19—**Evaluation and Management of Behavior Problems in the Elderly.** Thursday-Friday. Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 22-26—**Advances in Family Practice.** Monday-Friday. Child Development and Mental Retardation Center, Univ. of Wash., Seattle. Approximately 35 hrs. $100. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 25-26—**Immediate Care of the Sick and Injured.** Thursday-Friday. Univ. of Wash. Sch. of Med. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 1-2—**Clinical Pharmacology for the Practicing Physician.** Thursday-Friday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

April 9—**Gastroenterology for Non-Gastroenterologists.** Friday. Seattle. Location, hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 12-16—**Emergency Medicine Institute.** Monday-Friday. Univ. of Wash. Sch. of Med., Seattle. 38 hrs. $275. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 13, 20, 27—**Current Concepts in Nutrition.** Tuesdays for three weeks. Seattle. Location and fees to be determined. Contact Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 14, 21, 28—**Current Concepts in Nutrition.** Wednesdays for three weeks. Spokane. Location and fees to be determined. Contact Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 22-23—**Respiratory Care Conference.** Thursday-Friday. Seattle. Location, hours and fees to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 28-30—**Medicine and Law.** Wednesday-Friday. Seattle. Location, hours and fees to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 14-23—**Tax, Estate and Financial Planning.** Friday-Monday. Aboard the SS Rotterdam; 7-day cruise to Nassau and Bermuda. 25 hrs. $200. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

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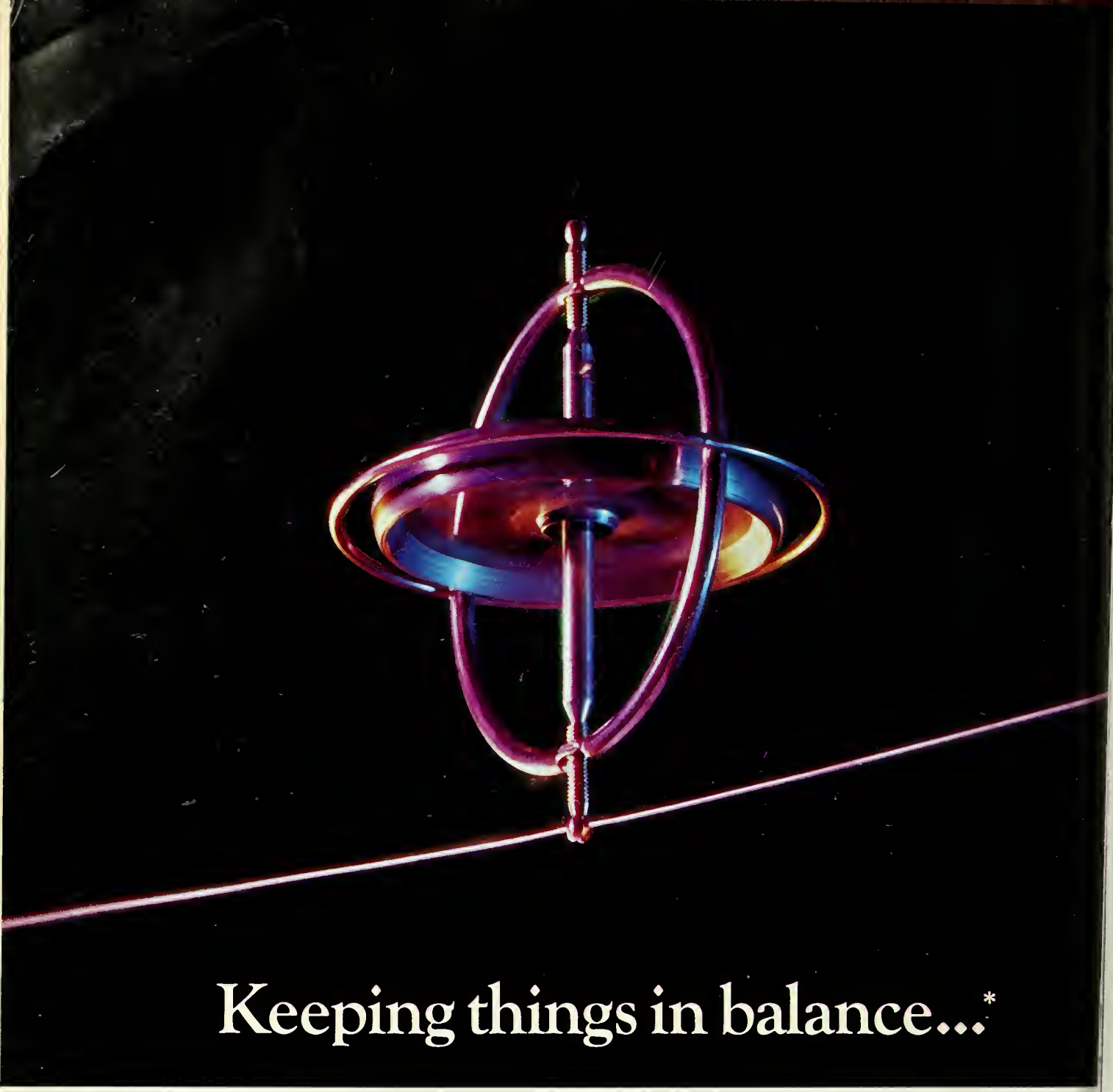

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Effective: Management of nausea and vomiting and dizziness associated with motion sickness.

Possibly Effective: Management of vertigo associated with diseases affecting the vestibular system.

Final classification of the less than effective indications requires further investigation.

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Meclizine HCl is contraindicated in individuals who have shown a previous hypersensitivity to it.

WARNINGS: Since drowsiness may, on occasion, occur with use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery.

Usage in Children: Clinical studies establishing safety and effectiveness in children have not been done; therefore, usage is not recommended in the pediatric age group.

Usage in Pregnancy: See "Contraindications."

ADVERSE REACTIONS: Drowsiness, dry mouth and, on rare occasions, blurred vision have been reported.

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Effectiveness across the spectrum of most common forms of insomnia

Awake too long, awake too often, awake too early...

These are the most common forms of insomnia, and may occur singly or in any combination. The night of troubled sleep depicted here comprises all three types. As the night progresses from left to right, each sleep stage is identifiable by its own shade of gray. Blue represents "Awake."

As you can see, this hypothetical "patient" takes well over an hour to fall asleep, awakens several times during the middle of the night and awakens too early in the morning.

Sleep Stages

- Awake
- REM
- Stage 1
- Stage 2
- Stage 3
- Stage 4

Awake too long

Awake too often during the night

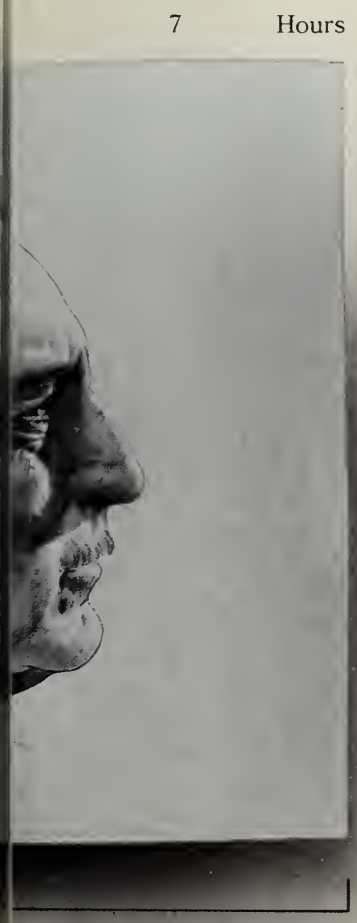
The insomnias most often occurring in young and older adults

For patients with trouble falling asleep (common in young adult insomnia patients), Dalmane (flurazepam HCl) 30 mg provides sleep within 17 minutes, on average. For those with trouble staying asleep or sleeping long enough (common in those over 50), Dalmane offers increased total sleep time with fewer nocturnal awakenings. These clinical results were demonstrated in studies conducted in four geographically separated sleep research laboratories.[1-4]

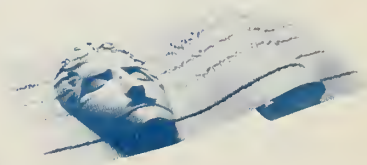
The relative safety of Dalmane (flurazepam HCl) is well documented

Dalmane (flurazepam HCl) is relatively safe and well tolerated; morning "hang-over" has been infrequent. The usual adult dosage is 30 mg; in elderly or debilitated patients, limit initial dosage to 15 mg to preclude over-sedation, dizziness or ataxia. Caution patients about possible combined effects with alcohol and other CNS depressants.

Broad-spectrum medication for the most common forms of insomnia



Awake too early



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- induces sleep rapidly
- reduces nighttime awakenings
- lengthens total sleep time

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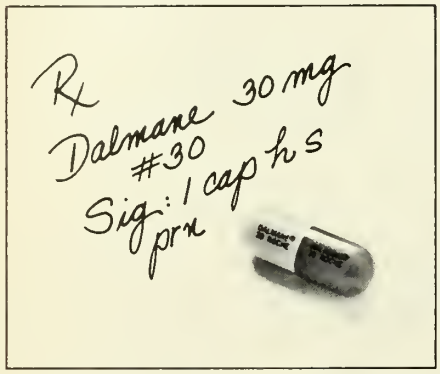

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- □ induces sleep within 17 minutes, on average
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- □ provides 7 to 8 hours sleep, on average, without repeating dosage

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Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

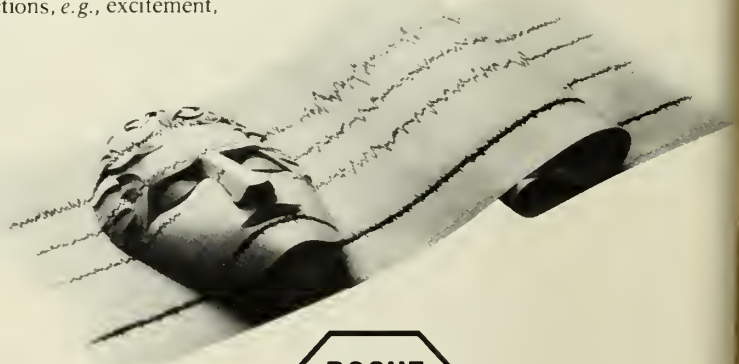
REFERENCES:

1. Karacan I, Williams RL, Smith JR: The sleep laboratory in the investigation of sleep and sleep disturbances. Scientific exhibit at the 124th annual meeting of the American Psychiatric Association, Washington DC, May 3-7, 1971

2. Frost JD Jr: A system for automatically analyzing sleep. Scientific exhibit at the 24th Clinical Convention of the American Medical Association, Boston, Nov 29-Dec 2, 1970; and at the 42nd annual scientific meeting of the Aerospace Medical Association, Houston, Apr 26-29, 1971

3. Vogel GW: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ

4. Dement WC: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ



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CONTRIBUTIONS OF "LETTERS TO THE EDITOR"

The Editorial Board will be glad to receive and consider for publication letters containing information of general interest to physicians or presenting constructive criticisms on issues of the day.

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Testing in Humans: Who, Where & When.

the weight of ethical opinion:

Few would disagree that the effectiveness and safety of any therapeutic agent or device must be determined through clinical research.

But now the *practice* of clinical research is under appraisal by Congress, the press and the general public. Who shall administer it? On whom are the products to be tested? Under what circumstances? And how shall results be evaluated and utilized?

The Pharmaceutical Manufacturers Association represents firms that are significantly engaged in the discovery and development of new medicines, medical devices and diagnostic products. Clinical research is essential to their efforts. Consequently, PMA formulated positions which it submitted on July 11, 1975, to the Subcommittee on Health of the Senate Labor and Public Welfare Committee, as its official policy recommendations. Here are the essentials of PMA's current thinking in this vital area.

1. PMA supports the mandate and mission of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and offers to establish a special committee composed of experts of appropriate disciplines familiar with the industry's research methodology to volunteer its service to the Commission.

2. PMA supports the formation of an independent, expert, broadly based and representative panel to assess the current state of drug innovation and the impact upon it of existing laws, regulations and procedures.

3. When FDA proposes regulations, it should prepare and publish in the *Federal Register* a detailed statement assessing the impact of those regulations on drug and device innovation.

4. PMA proposes that an appropriately qualified medical organization be encouraged to undertake a comprehensive study of the optimum roles and responsibilities of the sponsor and physician when company-sponsored clinical research is performed by independent clinical investigators.

5. PMA recognizes that the physician-investigator has, and should have, the ultimate responsibility for deciding the substance and form of the informed consent to be obtained. However, PMA recommends that the sponsor of the experiment aid the investigator in discharging this important responsibility by providing (1) a document detailing the investigator's responsibilities under FDA regulations with regard to patient consent, and (2) a written description of the relevant facts about the investigational item to be studied, in comprehensible lay language.

6. In the case of children, the sponsor must require that informed consent be obtained from a legally appropriate representative of the participant. Voluntary consent of an older child, who may be capable of understanding, in addition to that of a parent, guardian or other legally responsible person, is advisable. Safety of the drug or device shall have been assessed in adult populations prior to use in children.

7. PMA endorses the general principle that, in the case of the mentally infirm, consent should be sought from both an understanding subject and from a parent or guardian, or in their absence, another legally responsible person.

8. Pharmaceutical manufacturers sponsoring investigations in prisons must take all reasonable care to assure that the facilities and personnel used in the conduct of the investigations are suitable for the protection of participants, and for the avoidance of coercion, with a respect for basic humanitarian principles.

9. Sponsors intending to conduct non-therapeutic clinical trials through the participation of employee volunteers should expand the membership and scope of its existing Medical Research Committee, or establish such an internal Medical Research Committee, with responsibility to approve the consent forms of all volunteers, designs, protocols and the scope of the trial. The Committee should also bear responsibility to ensure full compliance with all procedures intended to protect employee volunteers' rights.

10. Where the sponsor obtains medical information or data on individuals, it shall be accorded the same confidential status as provided in codes of ethics governing health care professionals.

11. PMA and its member firms accept responsibility to aid and encourage appropriate follow-up of human subjects who have received investigational products that cause latent toxicity in animals or, during their use in clinical investigation, are found to cause unexpected and serious adverse effects.

12. PMA supports the exploration and development by its member companies of more systematic surveillance procedures for newly marketed products.

13. When a pharmaceutical manufacturer concludes, on the basis of early clinical trials of a basic new agent, that a new drug application is likely to be submitted, a proposed development plan accompanied by a summary of existing data, would be submitted to the FDA. Following a review of this submission, the FDA, and its Advisory Committee where appropriate, would meet with the sponsor to discuss the development plan. No *formal* FDA approval should be required at this stage. Rather, the emphasis should be on identification of potential problems and questions for the sponsor's further study and resolution as the program develops.

The PMA believes that health professionals as well as the public at large should be made aware of these 13 points in its Policy on Clinical Research. For these recommendations envisage constructive, cooperative action by industry, research institutions, the health professions and government to encourage creative and workable responses to issues involved in the clinical investigation of new products.

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(Continued on Page 16)

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Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

A TEXTBOOK OF RADIOLOGY—Second Edition—Edited by David Sutton, MD, FRCP, FFR, MCAR(Hon.), Director, Radiological Department, St Mary's Hospital, London, Consultant Radiologist, Maida Vale Hospital, London, Teacher in Radiology, St. Mary's Hospital Medical School, University of London, and Institute of Neurology, University of London; Assisted by Ronald G. Grainger, MD, FRCP, DMRD, FFR, Consultant Radiologist to United Sheffield Hospitals, Consultant Radiologist in Charge, Northern General Hospital, Sheffield. Longman Inc., Churchill Livingstone-Medical Division, 72 Fifth Avenue, New York City (10011), 1975. 1,376 pages, $79.50.

TUMOR SURGERY OF THE HEAD AND NECK—Robert S. Pollack, MD, Attending Surgeon, Presbyterian Hospital, San Francisco; Clinical Professor of Surgery and Oncology, University of the Pacific, San Francisco; Chief Consulting Surgeon, Veterans Administration Hospital, Martinez, and US Public Health Service Hospital, San Farncisco. S. Karger AG, Medical and Scientific Publishers, Arnold-Böcklin-Strasse 25, CH-4011 Basel, Switzerland, 1975. 206 pages, SFr. 73.-/ DM 70.-/ approx. US $29.50.

THE PHYSIOLOGY OF THE JOINTS—Annotated Diagrams of the Mechanics of the Human Joints—Second Edition—Volume 3: The Trunk and the Vertebral Column—I. A. Kapandji, Ancien Chef de Clinique Chirurgicale, Assistant des Hôpitaux de Paris; Translated by L. H. Honoré, B Sc, MB, Ch B. Churchill Livingstone, Edinburgh and London. Distributed in the United States of America by Longman Inc., 72 Fifth Avenue, New York City (10011), 1974. 251 pages, $14.00 (Paperback).

RETINA CONGRESS—25th Anniversary Meeting of the Retina Service, Massachusetts Eye and Ear Infirmary. Edited by Ronald C. Pruett, MD, Clinical Instructor in Ophthalmology, Harvard Medical School, Assistant Surgeon in Ophthalmology, Massachusetts Eye and Ear Infirmary, Clinical Senior Scientist, Retina Foundation, Boston; and Charles D. J. Regan, MD, Associate Professor of Ophthalmology, Harvard Medical School, Associate Chief and Surgeon in Ophthalmology, Massachusetts Eye and Ear Infirmary, Boston. Appleton-Century-Crofts, 292 Madison Avenue, New York City (10017), 1974. 730 pages, $45.00.

REVIEW OF ALLIED HEALTH EDUCATION: 1—General Editor: Joseph Hamburg, MD, Dean, College of Allied Health Professions, University of Kentucky; Associate Editors: Darrel J. Mase, PhD, Professor, Division of Health Systems Research, University of Florida College of Health Related Professions; and J. Warren Perry, PhD, Dean, School of Health Related Professions, State University of New York at Buffalo and Editor, **Journal of Allied Health.** The University Press of Kentucky, Lexington (40506), 1974. 234 pages, $7.50.

SIMPLIFIED MEDICAL RECORDS SYSTEM—A Directory of Medical Terminology—Burgess L. Gordon, MD, Visiting Professor of Medicine, Jefferson Medical College of Thomas Jefferson University, Consultant to the American Medical Association, Department of Current Medical Terminology. Publishing Sciences Group, Inc., 411 Massachusetts Avenue, Acton, MA (01720), 1975. 270 pages, $15.00.

STROKE AND ITS REHABILITATION—Volume 12 of Physical Medicine Library—Edited by Sidney Licht, MD, Curator, Physical Medicine, Collections, Yale University Medical Library, New Haven, Associate Professor, Medical Library Science, University of Miami; With 16 contributors. Elizabeth Licht, Publisher, P.O. Box J, New Haven, CT (06515), 1975. 562 pages, $20.00.

SYMPOSIUM ON RECONSTRUCTIVE HAND SURGERY—Volume IX. Editors: J. William Littler, MD, Chief of Plastic and Reconstructive Hand Surgery, Roosevelt Hospital, New York City; Lester M. Cramer, MD, Professor and Chairman, Section of Plastic Surgery, Temple University, Philadelphia; and James W. Smith, MD, Associate Professor of Plastic Surgery, The New York Hospital-Cornell Medical Center, New York City. The C. V. Mosby Company, 3301 Washington Boulevard, St. Louis, MO (63103), 1974. 324 pages, $42.50.

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Contraindications: Short acting estrogens are contraindicated in patients with (1) markedly impaired liver function; (2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal; (3) known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium; (4) thromboembolic disorders, thrombophlebitis, cerebral embolism, or in patients with a past history of these conditions; (5) undiagnosed abnormal genital bleeding.
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The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, estrogen therapy should be discontinued immediately.

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Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

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Because of individual variation in endogenous estrogen production, relative overdosage may occur which could cause undesirable effects such as abnormal or excessive uterine bleeding, mastodynia and edema.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

If unexplained or excessive vaginal bleeding should occur, reexamination should be made for organic pathology.

Pre-existing uterine fibromyomata may increase in size while using estrogens; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is incomplete.

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The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

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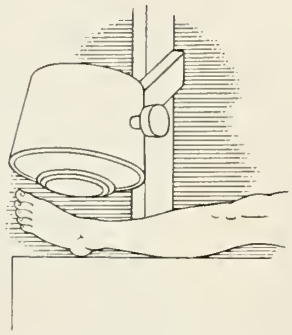
Facts about Scintiphotography



In recent years a variety of radiopharmaceuticals have been employed to aid in the diagnosis of bone and joint disorders. The joint-imaging technique consists of injecting technetium polyphosphate intravenously, and imaging is performed with the scintillation camera two hours after the administration of the radionuclide. In general, for joint surveying, the shoulders, elbows, hands, wrists, knees, ankles, feet, and vertebral column are mapped. The entire scanning process takes approximately one hour. The criterion for a positive image is a higher concentration of radioactivity in a joint region than in adjacent nonarticular bone. In effect, each patient serves as his own control.

INDOCIN®
(INDOMETHACIN | MSD)

helps relieve pain
and other symptoms
of inflammation
in acute
gouty arthritis
in selected patients

IMPORTANT NOTE: INDOCIN (Indomethacin, MSD) cannot be considered a simple analgesic and should not be used in conditions other than those recommended. The drug should not be prescribed for children because safe conditions for use have not been established.
Because of the high potency of the drug and the variability of its potential to cause adverse reactions, the following are strongly recommended: 1) the lowest possible effective dose for the individual patient should be prescribed. Increased dosage tends to increase adverse effects, particularly in doses over 150-200 mg per day, without corresponding clinical benefits; 2) careful instructions to, and observations of, the individual patient are essential to the prevention of serious and irreversible, including fatal, adverse reactions, especially in the aging patient.
Contraindications: Children 14 years of age and under; pregnant women and nursing mothers; active gastrointestinal lesions or history of recurrent gastrointestinal lesions; allergy to aspirin or indomethacin.
Warnings: *Gastrointestinal Effects:* Because of the occurrence and, at times, severity of gastrointestinal reactions, be continuously alert for any sign or symptom signaling a possible gastrointestinal reaction. The risks of continuing therapy with INDOCIN in the face of such symptoms must be weighed against the possible benefits to the individual patient. Gastrointestinal effects may be reduced by giving the drug immediately after meals, with food, or with antacids. Use greater care in aging patients.
Ocular Effects: Corneal deposits and retinal disturbances, including those of the macula, have been observed in some patients on prolonged therapy. Discontinue therapy if such changes are observed. Ophthalmologic examination at periodic intervals is desirable in patients on prolonged therapy.
Central Nervous System Effects: INDOCIN may aggravate psychiatric disturbances, epilepsy, and parkinsonism, and should be used with considerable caution in patients with these conditions. If severe CNS adverse reactions develop, discontinue the drug.
Precautions: Blurred vision may be a significant symptom that warrants a thorough ophthalmologic examination. Patients should be cautioned about engaging in activities requiring mental alertness and motor coordination, as driving a car. Headache which persists despite dosage reduction requires complete cessation of the drug. May mask the usual signs and symptoms of infection; therefore, the physician must be continually on the alert for this and should use the drug with extra care in the presence of existing controlled infection. After the acute phase of the disease is under control, an attempt to reduce the daily dose should be made repeatedly until the patient is off entirely.
Adverse Reactions: *Gastrointestinal Reactions:* Single or multiple ulcerations of the esophagus, stomach, duodenum, or small intestine, including perforation and hemorrhage, with fatalities in some instances; rarely, intestinal ulceration has been associated with stenosis and obstruction; gastrointestinal bleeding without obvious ulcer formation; perforation of preexisting sigmoid lesions (diverticulum, carcinoma, etc.); rarely, increased abdominal pain in ulcerative colitis patients or development of ulcerative colitis and regional ileitis; gastritis, which may persist after the cessation of the drug; nausea, vomiting, anorexia, epigastric distress, abdominal pain, and diarrhea.
Eye Reactions: Corneal deposits and retinal disturbances, including those of the macula, have been observed on prolonged therapy; blurring of vision.
Hepatic Reactions: Rarely, toxic hepatitis and jaundice, including some fatal cases.
Hematologic Reactions: Aplastic anemia, hemolytic anemia, bone marrow depression, agranulocytosis, leukopenia, and thrombocytopenic purpura. Since some patients manifest anemia secondary to obvious or occult gastrointestinal bleeding, appropriate blood determinations are recommended.
Hypersensitivity Reactions: Acute respiratory distress, including dyspnea and asthma; angiitis; pruritus; urticaria; angioedema; skin rashes; purpura.
Ear Reactions: Hearing disturbances, deafness, tinnitus.
Central Nervous System Reactions: Psychic disturbances including psychotic episodes, depersonalization, depression, and mental confusion; coma; convulsions; peripheral neuropathy; drowsiness; lightheadedness; dizziness; syncope; headache.
Cardiovascular-Renal Reactions: Edema, elevation of blood pressure, hematuria.
Dermatologic Reactions: Loss of hair, erythema nodosum.
Miscellaneous: Rarely, vaginal bleeding, hyperglycemia, glycosuria, ulcerative stomatitis, and epistaxis.
Note: In patients receiving probenecid, plasma levels of indomethacin are likely to be increased.
Supplied: Capsules containing 25 mg indomethacin each, in single-unit packages of 100 and bottles of 100 and 1000; capsules containing 50 mg indomethacin each, in single-unit packages of 100 and bottles of 100.
For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

MSD
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SHARP &
DOHME

DYAZIDE®

Trademark

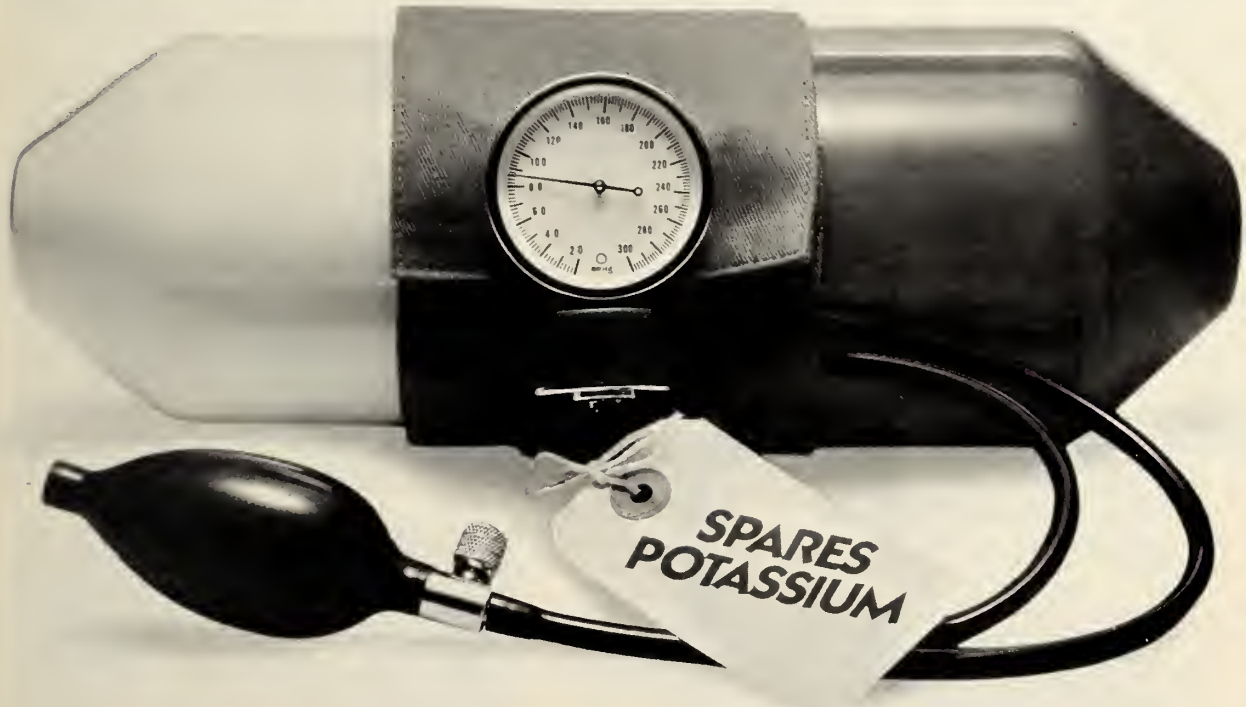
Each capsule contains 50 mg. of Dyrenium® (triamterene, SK&F) and 25 mg. of hydrochlorothiazide.

MAKES SENSE

TRIAMTERENE CONSERVES POTASSIUM WHILE HYDROCHLOROTHIAZIDE LOWERS BLOOD PRESSURE

FOR LONG-TERM CONTROL OF HYPERTENSION*

Serum K^+ and BUN should be checked periodically. (See Warnings Section.)



Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

* **Warning**
This fixed combination drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

***Indications:** *Edema:* That associated with congestive heart failure, cirrhosis of the liver, the nephrotic syndrome; steroid-induced and idiopathic edema; edema resistant to other diuretic therapy. *Mild to moderate hypertension:* Usefulness of the triamterene component is limited to its potassium-sparing effect.

Contraindications: Pre-existing elevated serum potassium. Hypersensitivity to either component. Continued use in progressive renal or hepatic dysfunction or developing hyperkalemia.

Warnings: **Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired.** Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, **check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently**—both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 capsules; in Single Unit Packages of 100 (intended for institutional use only).

SK&F Co., Carolina, P.R. 00630
Subsidiary of SmithKline Corporation

(Continued from Page 8)

PHYSICIANS WANTED

ORTHOPEDIST—Small growing Medical Group with industrial practice seeks board qualified Orthopedist. Surgery not required, malpractice insurance paid by group. Daytime only, no weekends. South Bay (Los Angeles) location. Partnership potential after one year. Contact Dr. Walker at (213) 731-0885.

DENVER, COLO.—INTERNIST OR FAMILY PHYSICIAN to join a solo MD in extremely large practice in ultra modern clinic; POMR, computer; major hospitals with medical school affiliation; Salary to $50,000 1st year depending on qualifications; must be aggressive and innovative and enjoy hard work; ample vacation and study time; opportunity for eventual takeover. Harold E. Gilman, MD, 3405 Downing, Denver, Colo. 80205; (303) 623-6171 or nite (303) 377-9373.

PATHOLOGISTS: The Department of Pathology at UCLA is willing to consider applications for appointment to the Clinical Staff on a volunteer basis. Applicants should have expertise in teaching and an interest in participating in the instructional program for the Second Year Medical and Dental Students as well as Interns and Residents of the department. UCLA is an Equal Opportunity/Affirmative Action Employer. Send Curriculum Vitae to J. L. Van Lancker, MD, Department of Pathology, University of California, Los Angeles, Los Angeles, CA 90024.

CHIEF OF RADIOLOGY: Highland General Hospital, an urban, public teaching hospital with large emergency and outpatient departments, seeks Board certified radiologist with administrative experience to head hospital Radiology Department. Salary $50,774 per year with prospective fee for service plan implementation by July 1, 1976. Personal interview required, at candidate's expense. Interested applicants refer reply to Director of Clinical Services, Highland General Hospital, 1411 E. 31st Street, Oakland, CA 94602; (415) 534-8055, Ext 522.

PHYSICIANS WANTED—ALL SPECIALTIES: Progressive city in Western North Dakota with college and recreational advantages. Area is wheat and oil country. Low crime rate and very few malpractice problems. Renumeration compares favorably with any section of the U.S. For information write: R & G Clinic, 109 West 7th St., Dickinson, N.D. 58601 or call (701) 225-6017, D. E. Wolf, MD.

GENERAL PRACTITIONERS, INTERNISTS, OB/GYN SPECIALISTS, and PEDIATRICIANS wanted immediately for new, 120 bed hospital in Northern Wisconsin community of 10,000. Reasonable liability insurance premiums! Great water sports, fishing, and hunting abound in this Lake Superior vacation area. Good schools and new office space available adjacent to hospital. Contact: Kenneth Morrow, MD, (715) 682-8146 after 7:00 p.m. or Lowell Miller (715) 682-4563 during normal working hours.

12-MAN MULTI-SPECIALTY CLINIC needs ophthalmologist, orthopedic surgeon, otolaryngologist, gynecologist and internist. The present group includes surgeons, internist, urologist, gynecologist and family practitioners. Northeastern Minnesota location with complete hospital facilities. Excellent recreational country, both summer and winter. Complete school system through junior college. Solid and growing economic conditions. No big city problems. Clinic paid profit sharing and pension plans. Malpractice insurance covered by clinic. Beginning salary open and depending upon background and specialty. Ownership participation after one year. Any questions you have will be answered immediately. Please reply—Mesaba Clinic, Hibbing, Minnesota 55746, or call Richard Moyer, MD; (218) 262-3441.

SURGERY RESIDENCY—G-IV position open in fully approved 5 year general surgery program utilizing county and private hospital facilities. Applications may be directed to: Executive Director, Tucson Hospitals Medical Education Program, P.O. Box 6067, Tucson, Arizona 85733.

(Continued on Page 28)

Center, Texas

PRACTICE OPPORTUNITY for family physician in east Texas community of 6,000 people. Located 60 miles from Shreveport, Louisiana and adjacent to the Toledo Bend Reservoir and Sam Rayburn Lake, the area provides abundant recreational activities. 60 bed JCAH approved hospital with 6 physicians serving a service area of 25,000. Physician office building under construction. Free inspection trip, relocation expenses and guarantee provided.

For further information call collect:

DON SCHAFFETT, Administrator,
Memorial Hospital of Center
P.O. Box 32
Center, Texas
(713) 598-2781

PHYSICIANS

Private practice (solo, partnerships, groups) opportunities exist in many communities of the Southeastern and Southwestern United States.

As a public service to the communities we serve, we are performing a free, no obligation, service acting as a liaison between physicians interested in practice opportunities and communities in need of their services. All communities have modern, JCAH approved hospitals, modern offices, and recognized needs for additional physicians.

For details call collect (615) 327-9551 or write with C.V. to:

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One Park Plaza
Nashville, Tennessee 37203

PHYSICIAN
Experienced in Teaching
Division of
INFECTIOUS DISEASES

This important opportunity is with York Hospital, a community 560-bed, JCAH-approved teaching hospital, in a beautiful section of Pennsylvania, 90 miles from Philadelphia. The position is responsible to the Departmental Educational Coordinator and Vice President of Medical Affairs.

Demonstrated teaching ability is necessary, with qualifications to provide guidance to education programs for medical students, house staff, and continuing education for attending staff. Liaison and coordinating will be maintained with medical colleges and community health agencies. Assessment and improvement of patient care will also be involved. Pennsylvania license, or eligibility, is necessary; Diplomate of the Board of Internal Medicine is preferred.

The position offers substantial salary, limited practice, liberal vacation, and excellent benefits, including 100 percent paid relocation. Please direct c.v. to M. S. Bacastow, MD, Vice President Medical Affairs, in confidence.

YORK HOSPITAL
York, Pennsylvania 17405

An Equal Opportunity Employer M/F

"Trauma and Emergency Surgery"

a postgraduate medical education course

presented by

The Division of Plastic and Reconstructive Surgery

of

STANFORD UNIVERSITY SCHOOL OF MEDICINE

AT STANFORD—MARCH 22 TO 26, 1976

The symposium will review the current status of management principles and procedures, including surgical techniques, applicable to the care of patients seen frequently in emergency rooms. The course has been designed to meet the needs of physicians and surgeons who are involved in emergency care, and is principally directed toward emergency room specialists, family and general practitioners.

Principal lecture sessions will cover topics of general interest, and a series of concurrent elective sessions will deal in depth with specialized subjects. Twenty-three hours of instruction will be provided.

Tuition for the course is $275 and advance registration is requested.

The Postgraduate Medical Education Program of Stanford University School of Medicine is fully accredited by the Council on Medical Education of the American Medical Association and by the California Medical Association.

For further information and a brochure of the course please contact:

The Division of Plastic and Reconstructive Surgery
Room R213, Stanford University School of Medicine
Stanford, CA 94305
Telephone (415) 497-5824

Schering

In serious gram-negative infections*

Three good reasons to initiate therapy with Garamycin® Injectable

(gentamicin sulfate)

1. Unique spectrum.

2. Incidence of bacterial resistance is low and has not increased significantly.

3. Relatively low order of adverse renal and eighth nerve reactions when used as directed.

*Due to susceptible organisms

1. Unique spectrum.

Garamycin Injectable (gentamicin sulfate) is active against susceptible strains of seven major gram-negative pathogens. These are:

Escherichia coli
Proteus, indole-negative
Proteus, indole-positive
Pseudomonas aeruginosa
Klebsiella
Enterobacter } species
Serratia

Garamycin Injectable is also highly effective against susceptible strains of **Staphylococcus aureus** and may be considered when penicillins are contraindicated.

Escherichia coli | *Proteus* species, indole-negative | *Proteus* species, indole-positive | *Pseudomonas aeruginosa* | *Klebsiella* | *Enterobacter* | *Serratia*

2. Incidence of bacterial resistance is low and has not increased significantly.

*In vitro** susceptibility virtually unchanged

* *In vitro* susceptibility data are not necessarily indicative of clinical effectiveness.

In a five-year study[1] in over 180 hospitals, gram-negative pathogens identified and tested demonstrated high susceptibility to GARAMYCIN. From 1971 through 1975 there was virtually no change in the percentage of strains of major gram-negative pathogens susceptible to GARAMYCIN.

In the seven or eight years' experience of one investigator[2] where gentamicin has been restricted to parenteral use, resistance has not appreciably changed.

Resistance has been demonstrated to develop slowly in stepwise fashion. No one-step mutations to high resistance have been reported.

References

1. P.M.R. Bacteriologic Reports—1971-1975.
2. Jackson, G.G.: Highlights of a Symposium on Gentamicin, a filmed panel discussion summarizing a symposium on gentamicin, University of California School of Medicine, Los Angeles, January 26, 1971.

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3. Relatively low order of adverse renal and eighth nerve reactions when used as directed.

Schering

Adverse renal reactions

The risk of adverse renal reactions is low in patients with normal renal function. Usually manifested by nitrogen retention as evidenced by a rising BUN and creatinine, they occur most often in patients with pre-existing renal damage and in patients receiving larger than recommended doses or treated for longer periods of time than recommended. See Warning Box below.

Adverse eighth nerve reactions

The incidence of adverse eighth nerve reactions with GARAMYCIN Injectable is relatively low. When occurring, the effect is predominantly on the vestibular branch of the eighth cranial nerve, resulting in vestibular dysfunction with vertigo and tinnitus. These symptoms have, in many cases, been transitory. The known effect on the auditory branch to date mostly has involved only the high-frequency hearing ranges. See Warning Box below.

A logical choice

in serious gram-negative infections†

- pneumonia
- urinary tract infections
- septicemia
- wound infections

† Due to susceptible organisms

Garamycin® I.M./I.V.

gentamicin sulfate 80mg/2ml.

injectable

40 mg /ml Each ml contains gentamicin sulfate equivalent to 40 mg of gentamicin

WARNING

Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug

Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable, usually for longer periods or with higher doses than recommended

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment

Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug

In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg /ml should be avoided

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity

USAGE IN PREGNANCY Safety for use in pregnancy has not been established

See Clinical Considerations section which follows

A logical choice
in serious gram-negative infections*

Schering

GARAMYCIN® Injectable, brand of gentamicin sulfate, U.S.P., injection, 40 mg. per ml.
Each ml. contains gentamicin sulfate, U.S.P. equivalent to 40 mg. gentamicin.
For Parenteral Administration.

WARNING

Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable usually for longer periods or with higher doses than recommended.

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Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY Safety for use in pregnancy has not been established.

INDICATIONS GARAMYCIN Injectable is indicated, with due regard for relative toxicity of antibiotics, in the treatment of serious infections caused by susceptible strains of the following microorganisms:

Pseudomonas aeruginosa, Proteus species (indole-positive and indole-negative), *Escherichia coli* and *Klebsiella-Enterobacter-Serratia* species.

Clinical studies have shown GARAMYCIN Injectable to be effective in septicemia and serious infections of the central nervous system (meningitis), urinary tract, respiratory tract, gastrointestinal tract, skin and soft tissue (including burns).

Bacteriologic tests to determine the causative organisms and their susceptibility to gentamicin should be performed.

Bacterial resistance to gentamicin develops slowly in stepwise fashion; there have been no one-step mutations to high resistance.

In suspected or documented gram-negative sepsis, GARAMYCIN may be considered as initial therapy. The decision to continue therapy with this drug should be based on the results of susceptibility tests, the severity of the infection, and the important additional concepts contained in the Warning Box.

For suspected sepsis when the infecting organism is unknown, gentamicin may be administered in conjunction with a penicillin-type drug. Following identification of the organism and its susceptibility, appropriate antibiotic therapy should then be continued. In the neonate with suspected sepsis or staphylococcal pneumonia, a penicillin-type drug is also usually indicated as concomitant therapy with gentamicin.

GARAMYCIN Injectable has been shown to be effective in serious staphylococcal infections. It may be considered in those infections when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility testing and clinical judgment indicate its use.

CONTRAINDICATIONS A history of hypersensitivity to gentamicin is a contraindication to its use.

WARNINGS See Warning Box.

PRECAUTIONS Neuromuscular blockade and respiratory paralysis have been reported in the cat receiving high doses (40 mg./kg.) of gentamicin. The possibility of these phenomena occurring in man should be considered if gentamicin is administered to patients receiving neuromuscular blocking agents, such as succinylcholine and tubocurarine.

Treatment with gentamicin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy is indicated.

ADVERSE REACTIONS:

Nephrotoxicity: Adverse renal effects, as demonstrated by rising BUN, NPN, serum creatinine and oliguria, have been reported. They occur more frequently in patients with a history of renal impairment treated with larger than recommended dosage.

Neurotoxicity: Adverse effects on both vestibular and auditory branches of the eighth nerve have been reported in patients on high dosage and/or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss.

Numbness, skin tingling, muscle twitching, and convulsions have also been reported.

Note: The risk of toxic reactions is low in patients with normal renal function who do not receive GARAMYCIN Injectable at higher doses or for longer periods of time than recommended.

Other reported adverse reactions, possibly related to gentamicin, include increased serum transaminase (SGOT, SGPT), increased serum bilirubin, transient hepatomegaly, decreased serum calcium; splenomegaly, anemia, increased and decreased reticulocyte counts, granulocytopenia, agranulocytosis, thrombocytopenia, purpura; fever, rash, itching, urticaria, generalized burning, joint pain, laryngeal edema; nausea, vomiting, headache, increased salivation, lethargy and decreased appetite, weight loss, pulmonary fibrosis, hypotension and hypertension.

DOSAGE AND ADMINISTRATION

GARAMYCIN Injectable may be given intramuscularly or intravenously.

For Intramuscular Administration:

Patients with normal renal function

Adults: The recommended dosage for GARAMYCIN Injectable for patients with serious infections and normal renal function is 3 mg./kg./day administered in three equal doses every 8 hours.

For patients weighing over 60 kg. (132 lb.), the usual dosage is 80 mg. (2 ml.) three times daily. For patients weighing 60 kg. (132 lb.) or less, the usual dosage is 60 mg. (1.5 ml.) three times daily.

In patients with life-threatening infections, dosages up to 5 mg./kg./day may be administered in three or four equal doses. This dosage should be reduced to 3 mg./kg./day as soon as clinically indicated.

In children and infants, the newborn, and patients with impaired renal function, dosage must be adjusted in accordance with instructions set forth in the Package Insert.

For Intravenous Administration:

The intravenous administration of GARAMYCIN Injectable is recommended in those circumstances when the intramuscular route is not feasible (e.g., patients in shock, with hematologic disorders, with severe burns, or with reduced muscle mass).

For intravenous administration in adults, a single dose of GARAMYCIN Injectable may be diluted in 100 or 200 ml. of sterile normal saline or in a sterile solution of dextrose 5% in water; in infants and children, the volume of diluent should be less. The concentration of gentamicin in solution in both instances should normally not exceed 1 mg./ml. (0.1%). The solution is infused over a period of one to two hours.

The recommended dose for intravenous administration is identical to that recommended for intramuscular use.

GARAMYCIN Injectable should not be physically premixed with other drugs, but should be administered separately in accordance with the recommended route of administration and dosage schedule.

HOW SUPPLIED GARAMYCIN Injectable, 40 mg. per ml., is supplied in 2 ml. (80 mg.) multiple-dose vials and in 1.5 ml. (60 mg.) and 2 ml. (80 mg.) disposable syringes for parenteral administration.

Also available, GARAMYCIN Pediatric Injectable, 10 mg. per ml., supplied in 2 ml. (20 mg.) multiple-dose vials for parenteral administration.

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AHFS Category 8:12.2

For more complete prescribing details, consult Package Insert or Physicians' Desk Reference. Schering literature is also available from your Schering Representative or Professional Services Department, Schering Corporation, Kenilworth, New Jersey 07033.

Garamycin® I.M./I.V.
gentamicin sulfate 80mg./2ml.
injectable
40 mg./ml. Each ml. contains gentamicin sulfate equivalent to 40 mg. of gentamicin.

*Due to susceptible organisms

SLS-595

STANFORD UNIVERSITY SCHOOL OF MEDICINE
OFFICE OF POSTGRADUATE MEDICAL EDUCATION

presents

BASIC SCIENCE FOR CLINICIANS

AT STANFORD UNIVERSITY • MARCH 1-5, 1976

This five-day interdepartmental course is a concise but comprehensive review of basic medical science and is designed to meet the needs of those clinicians who wish to expand their knowledge of molecular biology. Early registration is advised as attendance is limited. Tuition fee is $250 payable upon application for enrollment.

General lectures will cover a review of chemistry and physics for clinicians, chemical bonds of biological importance, subatomic particles, correlation of cell structure and function, the structure and function of proteins, sugars and lipids, the structure of nucleic acids, DNA synthesis, expression of genetic information, regulation of gene expression, evolution of proteins, carbohydrate and fat metabolism, bioenergetics, neuroendocrine relationships, neurobiology: structure and development, neurobiology: function, neurobiology: a cellular approach to the nervous system, mutagenic hazards.

Elective sessions will include the biology of water, structure of matter, bacterial antibiotic resistance, salt and water, interferon, blood coagulation, gastrointestinal immunity, energy supply and the design of the brain, tumor virus, genetics and disease, rheumatic disorders, organ morphogenesis, nutrition, enzymes and their actions, prostaglandins, atherosclerosis, hypertension, renin, and aldosterone, chromosomes and disease, mechanisms of immunity, genetics: problems and opportunities, nerve growth, hormones and their actions, molecular mechanisms of drug actions, biological membranes.

A faculty of 27 Stanford University biomedical scientists, including four Nobel Laureates, will take part in the program.

BASIC AND APPLIED PHARMACOLOGY

AT STANFORD UNIVERSITY • MARCH 29-APRIL 2, 1976

The objective of this five-day course is to familiarize physicians, and others involved in clinical pharmacology, with the concepts of modern drug use. The program includes an in-depth review of the basic principles and the practical aspects of drug action. **The course is intended to assist physicians in their daily clinical work.** Tuition fee is $250 payable upon enrollment, and advance registration is required.

Morning lectures will review important principles of chemistry and biochemistry and will deal with molecular mechanisms of drug actions; routes of administration; elimination, metabolism, and time course of drug action; toxicity and idiosyncrasy; tolerance and physical dependence; teratogenesis, mutagenesis, carcinogenesis; and drug interactions. Afternoon informal seminars will cover the rapidly changing field of applied pharmacology.

Forty-three faculty members of the Stanford University School of Medicine will participate.

IN HAWAII

MANAGEMENT OF THE SURGICAL PATIENT

AT MAUNA KEA BEACH HOTEL • MAY 1-8, 1976

This course is designed for all physicians, non-surgeons as well as surgeons, who participate in the care of surgical patients. It includes lectures and informal conferences dealing with the practical aspects of management of a variety of surgical problems, and an alternate series of concurrent sessions reviewing the fundamental concepts of molecular biology. In addition there will be seven problem-solving sessions on acid-base and blood gas disorders.

Tuition fee is $275, payable with $110 room deposit to Stanford University School of Medicine upon application for enrollment. Group flights departing Saturday, May 1, and returning Saturday, May 8, may be available from San Francisco and Los Angeles, as well as reduced tour airfares from other originating cities. Early application is advised.

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INJECTION

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In **Gonorrhea,** the drug regimen of choice is aqueous procaine penicillin G. In uncomplicated cases, administration of 4.8 million units together with 1 gram oral probenecid, given at least 30 minutes prior to injection, is recommended.

Indications: In treatment of moderately severe infections due to penicillin G-sensitive microorganisms sensitive to the low and persistent serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: When high sustained serum levels are required use aqueous penicillin G, IM or IV.

The following infection will usually respond to adequate dosages of intramuscular procaine penicillin G.—*N. gonorrhoeae:* acute and chronic (without bacteremia).

For deep intramuscular injection only.

Contraindication: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy.

Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Mental disturbances, including anxiety, confusion, agitation, depression, and hallucinations, have been reported in individuals following single-dose schedules for gonorrhea. Reactions have been transient, lasting from 15-30 minutes.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 cc. of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparations should not be used. Antihistaminics appear beneficial in treatment of procaine reaction.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy, discontinue penicillin and take appropriate measures.

If allergic reaction occurs, withdraw penicillin unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to penicillin therapy.

When treating gonococcal infections with suspected primary or secondary syphilis, perform proper diagnostic procedures, including darkfield examinations. In all cases in which concomitant syphilis is suspected, perform monthly serological tests for at least four months.

Adverse Reactions: (Penicillin has significant index of sensitization) skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; serum sickness-like reactions, including chills, fever, edema, arthralgia and prostration. Severe and often fatal anaphylaxis has been reported. (See "Warnings.")

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Dosage and Administration: Administer only by *deep intramuscular injection,* in upper outer quadrant of buttock. In infants and small children, midlateral aspect of thigh may be preferable. When doses are repeated, vary injection site. Before injection, aspirate to be sure needle bevel is not in blood vessel. If blood appears, remove needle and inject in another site.

Although some isolates of *Neisseria gonorrhoeae* have decreased susceptibility to penicillin, this resistance is relative, not absolute, and penicillin in large doses remains the drug of choice. Physicians are cautioned not to use less than recommended doses.

Gonorrheal infections (uncomplicated)—Men or Women: 4.8 million units intramuscularly divided into at least two doses and injected at different sites at one visit, together with 1 gram of oral probenecid, preferably given at least 30 minutes prior to injection.

NOTE: Treatment of severe complications of gonorrhea should be individualized using large amounts of short-acting penicillin. Gonorrheal endocarditis should be treated intensively with aqueous penicillin G. Prophylactic or epidemiologic treatment for gonorrhea (male and female) is accomplished with same treatment schedules as for uncomplicated gonorrhea.

Retreatment: The National Center for Disease Control, Venereal Disease Branch, U.S. Dept. H.E.W. recommends:

Test cure procedures at approximately 7-14 days after therapy. In the male, a gram-stained smear is adequate if positive; otherwise, a culture specimen should be obtained from the anterior urethra. In the female, culture specimens should be obtained from both the endocervical and anal canal sites.

Retreatment in males is indicated if urethral discharge persists 3 or more days following initial therapy and smear or culture remains positive. Follow-up treatment consists of 4.8 million units aqueous procaine penicillin G, I.M. divided in 2 injection sites at single visit.

In uncomplicated gonorrhea in the female, retreatment is indicated if follow-up cervical or rectal cultures remain positive for *N. gonorrhoeae.* Follow-up treatment consists of 4.8 million units aqueous procaine penicillin G daily on 2 successive days.

Syphilis: all gonorrhea patients should have a serologic test for syphilis at the time of diagnosis. Patients with gonorrhea who also have syphilis should be given additional treatment appropriate to the stage of syphilis.

Composition: Each disposable syringe 2,400,000 units (4-cc. size) contains procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer, and as w/v approximately 0.5% lecithin, 0.5% carboxymethylcellulose, 0.5% povidone, 0.1% methylparaben, and 0.01% propylparaben. The multiple-dose 10-cc. vial contains per cc. 300,000 units procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer and approximately 7 mg. lecithin, 2 mg. carboxymethylcellulose, 3 mg. povidone, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben, and 0.14 mg. propylparaben.

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In the long run, a populace educated to the risks and prevention of VD is probably the best answer to the problem. Meanwhile, though, adequate doses of the recommended types of penicillin remain a formidable weapon.

IN SYPHILIS
INJECTION
Bicillin® L-A
(STERILE BENZATHINE PENICILLIN G SUSPENSION) WYETH

Syphilis is preferably treated with benzathine penicillin G, which is also the drug of choice for prophylaxis after exposure. Administration of 2.4 million units (1.2 million in each buttock) usually cures most cases of primary, secondary and latent syphilis with negative spinal fluid.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular benzathine penicillin G.—Venereal infections: Syphilis, yaws, bejel and pinta.

For deep intramuscular injection only.

Contraindication: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens.

Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms including fungi. Take appropriate measures should superinfection occur.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness-like reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high doses of parenteral penicillin.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Dosage and Administration: Venereal infections—

Syphilis—Primary, secondary and latent—2.4 million units (1 dose).

Late (tertiary and neurosyphilis)—2.4 million units at 7 day intervals for three doses.

Congenital—under 2 years of age, 50,000 units/Kg. body weight; ages 2-12 years, adjust dosage based on adult dosage schedule.

(Shake multiple-dose vial vigorously before withdrawing the desired dose.) Administer by **deep intramuscular injection** in the upper outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site. Before injecting the dose, aspirate to be sure needle bevel is not in a blood vessel. If blood appears, remove the needle and inject in another site.

Composition: Units benzathine penicillin G (as active ingredient): 2,400,000 units in 4-cc. single dose disposable syringe. Each disposable syringe also contains in aqueous suspension with sodium citrate buffer, as w/v approximately 0.5% lecithin, 0.6% carboxymethylcellulose, 0.6% povidone, 0.1% methylparaben, and 0.01% propylparaben. 300,000 units per cc.—10-cc. multi-dose vial. Each cc. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. povidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben, and 0.14 mg. propylparaben.

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*U.S. Dept. of Health, Education, and Welfare: VD Fact Sheet 1972. Publication No. (HSM) 73-8195.

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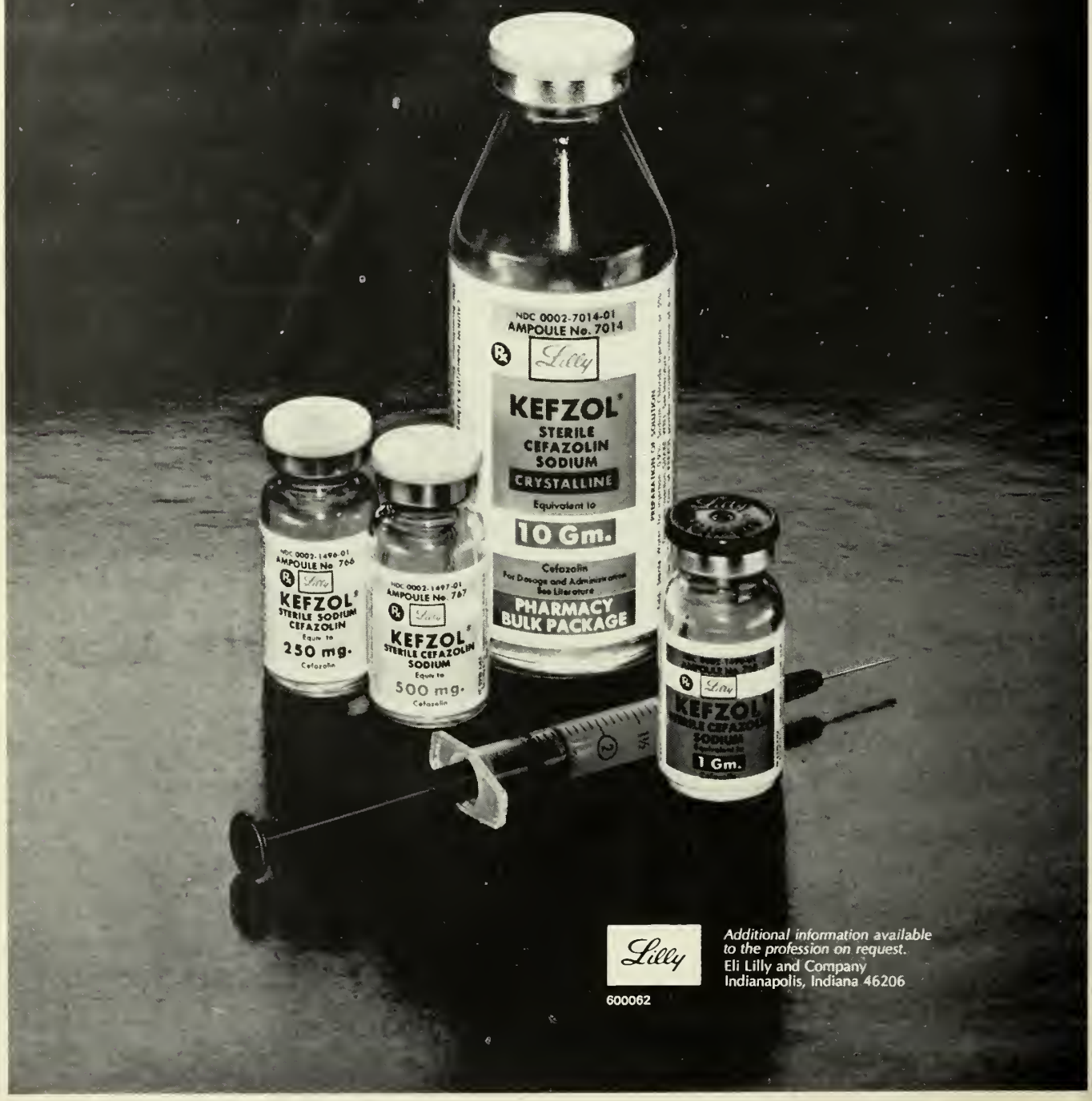

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Refer to: Calcaterra TC, Hepler RS: Antral-ethmoidal decompression in Graves' disease—Five-year experience. West J Med 124:87-91, Feb 1976

THE WESTERN
Journal of Medicine

Antral-Ethmoidal Decompression in Graves' Disease

Five-Year Experience

THOMAS C. CALCATERRA, MD, *and* ROBERT S. HEPLER, MD, *Los Angeles*

The orbital manifestations of Graves' disease frequently constitute the major and distressing portion of the morbidity in this poorly understood process. Patients with optic neuropathy, exposure keratopathy or disfiguring proptosis may be aided considerably by decompression to permit swollen orbital contents to move into the maxillary and ethmoid sinus cavities. Experience with 38 patients treated over a five-year period indicates that antral-ethmoidal decompression is a logical, successful form of therapy and generally free of serious complications. It may provide benefit earlier in the course of Graves' exophthalmopathy than has been accepted in the past.

PATHOGENESIS AND TREATMENT of ophthalmopathy associated with Graves' disease remain poorly understood. The major clinical problems in the treatment of patients arise from the often extreme hypertrophy of orbital muscles and fat, which, together, produce increased intraorbital pressure and forward displacement of the eyes. Proptosis of the globes may lead to a variety of difficulties that range in severity from cosmetic disfigurement to permanent blindness. Medical, radiotherapeutic and surgical measures have been used in an attempt to lessen the exophthalmos, with varying degrees of success. It appears that one reliable method consists of antral-ethmoidal decompression of the orbital contents. The authors' personal experience employing this operative treatment in 38 patients provides the basis for this report.

Despite extensive experimental investigation, no specific antibody or hormone has been proved to be responsible for the ophthalmopathy of Graves' disease. Even the relationship to the patient's hyperthyroidism is confusing, since the exophthalmos may develop before, during or after the hyperthyroid state and frequently appears after the hyperthyroidism has been treated and the patient returned to a euthyroid state.

Degree of proptosis is not a reliable indicator of the severity of the disease and the risk to vision. Variability in effect upon the ocular structures may be related to individual differences, such as tightness of the orbital septum and lids, tension of the rectus muscles and length of the optic

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Submitted July 10, 1975.

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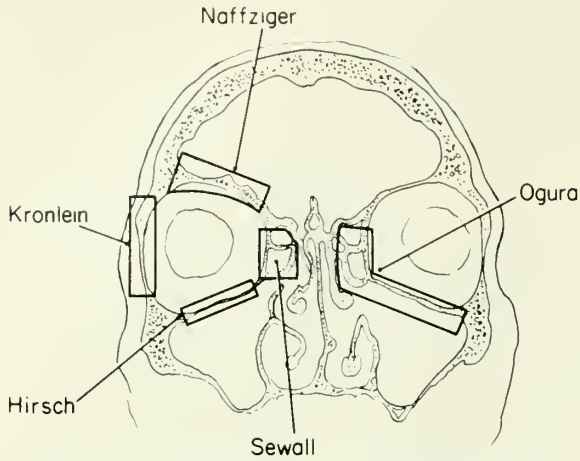

Figure 1.—Coronal section of skull showing the portions of orbit removed in various methods used for decompression.

nerve. Enlargement of the extraocular muscles, up to as much as eight times their normal size, occurs with the deposition of mucopolysaccharides; in addition, the orbital adipose tissue becomes edematous. Chronic inflammatory cell infiltration and fibrosis of the muscles may occur, particularly in later stages of the disorder.

Dollinger[1] first reported orbital decompression by removal of the lateral wall of the bony orbit (Kronlein's operation) to allow the orbital contents to herniate into the temporal fossa. Two decades later, Naffziger[2] published the first report of decompression of the orbital contents into the anterior cranial fossa by a transcranial approach. Use of the paranasal sinus cavities to decompress the orbit was described by Sewall[3] who removed the common wall between the ethmoid sinuses and the orbit to provide a medial decompression. Hirsch[4] later reported inferior decompression into the maxillary sinus achieved by removal of the orbital floor. Walsh and Ogura[5] combined the operations of Hirsch and Sewall, removing both the medial and inferior walls of the orbit (Figure 1). The antral-ethmoidal method of orbital decompression was the operation used in this study group.

Methods and Material

Between January 1970 and January 1975, 38 patients with Graves' exophthalmopathy were treated at the University of California, Los Angeles, Hospital by the antral-ethmoidal decompression method. All patients received ophthalmologic evaluation before and after operation and were followed for a minimum of six months.

Surgical Indications

Patients in the study series had a variety of signs and symptoms, most of which appeared to be related to increased orbital pressure. Most complained of excessive tearing and photophobia. The more serious symptoms of ocular pain and decreased vision usually reflected either exposure keratitis or optic neuropathy. Diplopia was seen frequently in patients with severe proptosis and in those in the later stages of the disorder.

In 21 of the patients (55 percent), there was some degree of optic neuropathy manifested by reduced vision with clinical signs of optic nerve dysfunction. Some, but not all, of these patients with optic neuropathy had visible optic nerve head swelling. Five patients with optic neuropathy and seven without had exposure keratopathy refractory to treatment with artificial tears and ocular lubricant ointments. Ten patients without keratopathy or optic neuropathy underwent decompression, primarily for cosmetic reasons or because of severe ocular discomfort. Almost all patients had evidence of extraocular muscle weakness, but less than a third (11 patients) had persistent and troublesome diplopia preoperatively.

Duration of time from onset of exophthalmos to operation varied from three months to nine years. Vision-threatening complications were present in those patients with shorter preoperative intervals, whereas cosmetic considerations were generally primary when the proptosis was longstanding. Of the patients, 34 had received steroid therapy during the course of the illness, and 22 were receiving steroids at the time of operation. In most patients, the systemic steroids relieved the ocular symptoms initially, but either a recurrence of the original ocular problems or a complication of the steroid treatment necessitated its discontinuation.

Surgical Technique

Clinical hyperthyroidism is corrected medically, with ^{131}iodine in some patients, whenever possible before operation. Documentation of adequate sinus pneumatization and freedom from inflammatory disease is ascertained by sinus x-ray films. Patients currently or recently receiving systemic steroids are prepared by parenteral corticosteroids given on the evening and morning before operation.

Decompression is carried out with the patient under general endotracheal anesthesia in a semi-

Figure 2.—Preoperative and postoperative frontal and lateral views of a patient with Graves' disease treated by antral-ethmoidal decompression. Recession of 6.5 mm was achieved.

sitting position. The legs are wrapped with elastic bandages to prevent venous pooling. The eyes remain uncovered so that they may be observed during the operative procedure. A sublabial incision is made to approach the maxillary and ethmoid sinuses. Ethmoid cells are exenterated to the cribriform plate with the anterior and posterior ethmoidal arteries used as landmarks. The orbital floor and lamina papyracea are fractured in an eggshell fashion and removed, while the orbital periosteum, infraorbital nerve and orbital rim are preserved. Orbital periosteum sags considerably after the removal of bone. Additional resection may be achieved by incision of the orbital periosteum with radial cuts, allowing the orbital fat to herniate through the incision. The effect is monitored by a gas sterilized exophthalmometer, the number and extent of the periosteal incisions being increased until the desired level of recession in achieved.[6] The orbit with the most proptotic eye is approached first, preserving at least some periosteal support. Then the opposite, less proptotic orbit is decompressed until the two eyes are approximately equal. In no instance is periorbital fat dissected from around the muscles. It is important to anticipate and allow for the additional 1 to 2 mm of recession that develops invariably within the first postoperative month. A conventional nasal antrostomy is created through the inferior meatus of the nose. The entire procedure may be done upon both orbits in about an hour, and the patient is usually discharged on the second postoperative day.

Results

The average recession achieved was 4.2 mm, with the range between 2 and 9 mm. In general, the greater the proptosis, the greater was the achieved recession of the globe (Figures 2 and 3). In some instances in which the exophthalmos was long-standing, the periorbital fat was fibrotic and had limited tendency to herniate through the periorbital incisions, reducing the effect of the procedure.

All patients with exposure keratitis were improved sufficiently to discontinue local medical management. Some improvement in vision was noted in almost all patients with short-term neuropathy. Visual return, which was occasionally dramatic, was usually noted in the immediate postoperative period and was assumed to be secondary to the decrease in orbital pressure. Five patients had either little improvement in vision or a delayed decrease in visual acuity that was managed by irradiation therapy in three patients and intermittent steroid therapy in the other two patients.

Decompression for cosmetic purposes was successful as a single operation when there was no

Figure 3.—Views of another patient in the series showing operative results with 6 mm of recession obtained.

significant lid retraction. Levator spasm did not improve after decompression, and two patients required additional operative procedures to lengthen the levator muscle. In only one patient without preoperative diplopia did double vision develop postoperatively, and the disturbance was limited to upward gaze. Five patients with preoperative diplopia underwent subsequent extraocular muscle operation. In these five patients, the prior decompression of the orbit appeared to facilitate the muscle procedure, and in all five patients the diplopia was improved or cured.

Complications

Late recession of the orbital contents resulted in relative enophthalmos in two patients that was of sufficient magnitude to permit the lower arc of the corneal scleral limbus to become covered by the lower lid. Recurrent maxillary sinusitis in one patient resolved after revision of the naso-antral window. Diplopia on upward gaze that had not been present preoperatively developed in one patient. All patients experienced temporary numbness of the cheek and upper lip, attributable to traction on the inferior orbital nerve, but normal sensation generally returned by three months. In no patient was numbness permanent. There were no instances of either fracture of the cribriform plate with cerebrospinal fluid leakage or injury to the optic nerve as a result of the surgical procedure.

Discussion

Patients with dysthyroid ophthalmopathy are seen with a spectrum of ocular involvement. Some can be managed conservatively with eye drops and eyelid closure with tape at night. However, when vision is threatened by exposure keratopathy or optic neuropathy, more vigorous treatment is indicated. Unfortunately, systemic corticosteroids usually provide only temporary remission, and local repository placement of corticosteroid material within the orbit is a relatively new and controversial form of therapy.

Antral-ethmoidal decompression has the advantage of utilizing an air-containing space, therefore achieving more effect than is possible with either a lateral or a superior (cranial) decompression. In both such approaches, soft tissue compromises the space available for orbital recession, and more than 3 mm of recession can seldom be accomplished. The antral-ethmoidal approach, on the other hand, permits as much as 11 mm, and the amount of recession can be controlled. The cranial approach is an extensive procedure with a small but significant risk of intracranial complications and requirement for prolonged postoperative care. In addition, pulsations transmitted to the globe from the intracranial tissues may be annoying to the patient. The lateral approach requires a facial incision that extends posteriorly from the lateral canthus.

None of the decompressive operations correct

diplopia in any predictable manner, because they do not influence the myopathy that is primarily responsible for diplopia in Graves' disease. In fact, diplopia may be even more troublesome to a patient after a decompressive procedure, particularly if visual acuity is substantially improved. A planned ocular muscle surgical procedure after decompression is facilitated because the eye is restored to a more normal position, and tension on already damaged muscles is reduced, allowing more precise muscle manipulation.[7]

Until more specific therapy is discovered to prevent or reverse the orbital complications of Graves' disease, some patients will require orbital decompression. Whereas this surgical procedure was once reserved for patients with advanced disease, particularly those with threatened blindness, our experience with antral-ethmoidal decompression indicates that use of the procedure is reasonable at less advanced stages of the disease and is very likely preferable to long-term high dosage steroid therapy. In those patients with severe proptosis without visual impairment, antral-ethmoidal decompression offers a satisfactory method of providing substantial improvement in a disfigured appearance.

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Combining Pseudopregnancy with Surgery for Endometriosis

. . . At present the only indication in my mind for the use of preoperative pseudopregnancy is if there is extensive fixation of the uterus in third degree retroversion, extensive ovarian endometriosis with fixation of the tube and with the thought that I am going to have a very difficult dissection and I may have a very difficult time with preservation of the structures. With these patients, I utilize either norethynodrel with mestranol (Enovid-E®) or norethynodrel with ethinyl estradiol (Ovral®) in pseudopregnancy form for 8 to 12 weeks preoperatively. Postoperative pseudopregnancy, I think, is indicated only in those patients who have residual endometriosis—for example, on the bladder serosa or on the bowel ilia, the large bowel—at the termination of the surgical procedures. If I am confident that I have excised . . . all areas of endometriosis and I have adequately peritonealized all of these areas, I do not believe that the postoperative use of pseudopregnancy is advantageous.

—ROBERT W. KISTNER, MD, *Boston*
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Refer to: Moore TM, Harvey JP Jr: The management of benign bone lesions. West J Med 124:92-98, Feb 1976

The Management of Benign Bone Lesions

TILLMAN M. MOORE, MD, *and* J. PAUL HARVEY, JR., MD, *Los Angeles*

The almost bewildering variety of lesions that can affect bone contrasts sharply with the limited potential of bone to differentially respond to those lesions. This paradox can create a challenging problem when a bone lesion is shown on an x-ray film. Although heavily populated with pleuripotential primitive mesenchymal cells, there is seldom a histologic or radiographic change in the involved bone specific enough to allow a comfortable diagnostic autonomy to be enjoyed by surgical pathologists, radiologists or orthopaedic surgeons. Even when diligent and astute clinical evaluation has excluded infectious, parasitic, metabolic and metastatic causes of the change seen on x-ray studies, a physician is often still uncertain as to the exact nature of the lesion. A knowledge of the relative frequency of the common lesions, an acceptance that biopsy studies and treatment must be combined at times, an appreciation of the possibility of malignant change in a given lesion and a tendency to seek early consultation will likely lead to timely and accurate diagnosis. Once the diagnosis is made, optimum management must be selected. The best current opinion categorizes the lesions into treatment groups consisting of observation, curettage and graft, block excision, cryotherapy and radiotherapy.

ELECTRON MICROSCOPY, angiography and histochemical studies continue to contribute to the understanding of benign bone lesions. This type of information is valuable in view of our limited knowledge of these lesions but is not yet clinically helpful except in contributing to diagnostic certainty and providing a basis for controversy. The underlying nature of these lesions, often loosely called "tumors," is uncertain both for the true neoplasms and the other lesions which may closely resemble them radiographically. Because some of the benign bone lesions are seen infrequently even in large centers, clinical studies have necessarily been retrospective, and valid patterns of natural history emerge slowly. Concepts of management of benign bone tumors are therefore changing and information with which to develop an appropriate plan of management of a particu-

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lar lesion is not always readily available. A schema has been developed that reflects current opinion and can be used as a general guide to clinical management.

"Tumor" Entities

From a pragmatic viewpoint, the list of benign "tumors" of bone will necessarily include a wide variety of lesions, even if the metabolic, inflammatory and dysplastic lesions are excluded (Table 1).

In Table 1 the more common benign bone "tumors" are listed on the left in rough order of descending frequency. Parosteal or juxtacortical variants are excluded for brevity.

Fibrous cortical defects are certainly the most common.[1-5] One or more fibrous cortical defects (or nonossifying fibromata) occur in the first decade of life in more than a third of all children.[6,7] The least frequent of the common lesions is the chondromyxoid fibroma with less than 200 reported in the world's literature.[8,9] The giant cell tumor of bone, which in the past has been considered a benign neoplasm with occasional fatal dissemination,[10,11] is excluded from this list. The giant cell tumor is at least "quasi-malignant"[12] and its malignant behavior, regardless of histologic grade, in up to 30 percent of cases[13,14] indicates that it should be approached as a low grade but fully malignant neoplasm.[15]

A much rarer group of lesions, listed on the right of Table 1, are true tumors in the neoplastic sense. All the tumors listed in the "rare" category have been described at least twice in the English language literature. An additional number of exceedingly rare isolated lesions have also been described, but are omitted for brevity.

TABLE 1.—*Benign Lesions of Bone*

Common Lesions	*Rare Lesions*
1. Fibrous cortical defect	17. Hemangioma
2. Nonossifying fibroma	18. Lymphangioma
3. Osteochondroma	19. Osteoma
4. Bone island	20. Lipoma
5. Paget's disease	21. Neurofibroma
6. Unicameral bone cyst	22. Desmoplastic fibroma
7. Bone infarct	23. Ossifying fibroma
8. Myositis ossificans	24. Fibromyxoma
9. Fibrous dysplasia	25. Fibroxanthoma
10. Enchondroma	26. Periosteal desmoid
11. Osteoid osteoma	27. Periosteal chondroma
12. Eosinophilic granuloma	28. Neurilemoma
13. Aneurysmal bone cyst	29. Glomus tumor
14. Chondroblastoma	30. Cementoma
15. Osteoblastoma	31. Hemangiopericytoma
16 Chondromyxoid fibroma	32. Ganglioneuroma

Giant cell tumor is excluded because of its basically malignant nature. Infectious, parasitic and metabolic disease and their associated bone lesions are excluded.

Malignant Potential of Common Benign "Tumors" of Bone

The frequency with which a benign bone lesion may become a malignant lesion varies from zero in the case of osteoid osteoma[1] to 50 percent with multiple enchondromas.[5] The number and diversity of malignant lesions associated with other benign lesions is interesting (Table 2). In Table 2, the list of common benign bone lesions has been condensed from 16 to 14 by omitting bone island and combining the histiologically identical nonossifying fibroma with fibrous cortical defect. The 14 entities can then be arranged into three general categories—acquired, developmental and neoplastic.

TABLE 2.—*Malignant Lesions Associated with Benign Lesions*

Benign "Tumor" of Bone	*Cause*	*Reported Malignancy*
Aneurysmal bone cyst	Acquired	None
Unicameral bone cyst	Acquired	Chondrosarcoma (Grabias and Mankin[21]) and fibrosarcoma, giant cell tumor, osteosarcoma (Johnson, et al[20])
Myositis ossificans	Acquired	None? (Pack and Braund;[22] Shanoff, et al[23])
Bone infarct	Acquired	Fibrosarcoma (Dorfman, et al;[25] Furey, et al[24])
Eosinophilic granuloma	Acquired	Letterer-Siwe? (Lieberman, et al[29])
Fibrous cortical defect	Developmental	None? (Bhagwandeen[34])
Osteochondroma	Developmental	Chondrosarcoma, osteosarcoma (Dahlin[35])
Enchondroma(ta)	Developmental	Chondrosarcoma
Fibrous dysplasia	Developmental	Osteosarcoma, chondrosarcoma, fibrosarcoma, adamantinoma (Cohen, et al[43])
Paget's disease	Developmental?	Osteosarcoma, chondrosarcoma, fibrosarcoma, giant cell tumor
Osteoid osteoma	Neoplastic	None
Osteoblastoma	Neoplastic	None? (Mayer[57])
Chondroblastoma	Neoplastic	Malignant chondroblastoma, chondrosarcoma (Kahn;[59] Sweetnam and Ross[58])
Chondromyxoid fibroma	Neoplastic	Chondrosarcoma (Iwata and Coley;[65] Levy[66])

Acquired Lesions

The cause of an aneurysmal bone cyst is unknown. It is included in this category because of its occasional association with another of the benign tumors,[16] suggesting it may result from degeneration of an underlying lesion and development of arteriovenous fistulae or at least local alteration of hemodynamics.[17]

The unicameral bone cyst and the lesions listed as myositis ossificans[5] are definitely acquired.[18,19] The occurrence of malignancy arising in both unicameral bone cysts[20,21] and myositis ossificans[22,23] has been reported.

Sarcoma has been reported as a complication of bone infarct.[24,25]

Eosinophilic granuloma is of unknown cause. If the concept of histiocytosis as expressed in the past[26-28] is valid then Hand-Schüller-Christian disease and particularly Letterer-Siwe disease[29] might be considered the malignant counterparts as indicated. There is considerable recent opinion to suggest that the contrary is true, however.[30,31] Letterer-Siwe disease may, at times, include lymphomatous disorders.[29]

Developmental Lesions

The fibrous cortical defect is listed among this group[32,33] despite the fact that its occasional evolution into a nonossifying fibroma might suggest that the latter is neoplastic.[5] Malignancy has been recorded in one case,[34] but that occurred within 18 months and the initial x-ray findings were not compatible with a nonossifying fibroma, placing the original diagnosis in doubt.

Chondrosarcomatous degeneration of an osteochondroma occurs in at least 20 percent of cases in the multiple familial type but probably less than 1 percent of the isolated lesions.[1,5,35] The apparent development of two cases of osteosarcoma arising in osteochondroma has been reported.[35]

Both solitary and multiple enchondromata are placed in the developmental group. Although Jaffe is noncommittal about the nature of the usual solitary enchondroma, the multiple types in Ollier's and Mafucci's syndromes are stated to be definitely developmental.[5] Malignant transformation of a single enchondroma is infrequent in large tubular bones,[5] and rare in the phalanges,[1] but has been reported. Spratt's calculation of doubling time of chondrosarcomata suggests that these more slowly growing malignant tumors may be present at birth, or congenital.[37] Chondrosarcoma occurs probably in over 50 percent of cases of multiple enchondromata[5] except in Mafucci's syndrome which has approximately the same incidence of malignant degeneration as the multiple osteochondromata.[38]

The occasional monomelic or ipsilateral distribution of bone lesions and the association of skin pigmentation which is occasionally present at birth indicate that fibrous dysplasia is developmental. Furthermore, the bone dysplasia tends to become quiescent when adulthood is reached, at least in the monostotic type.[39] Osteosarcoma, fibrosarcoma and chondrosarcoma have occasionally developed in bones affected with lesions of fibrous dysplasia[40,41] both in irradiated and nonirradiated bone. About 0.5 percent of cases of fibrous dysplasia will develop a bone sarcoma, 400 times the spontaneous rate.[42] Adamantinoma has also been reported in bones showing lesions microscopically compatible with fibrous dysplasia but separated from them.[43]

Barry[44] tends to reject the hereditary nature of Paget's disease reported by others.[45-49] In patients with Paget's disease, sarcomatous degeneration is expected in fewer than 1 percent of asymptomatic cases[50,51] but in up to 10 percent of symptomatic cases.[5,52] Schmorl[53] and Collins[54] have reported more than a 3 percent incidence of Paget's disease in autopsies of patients over the age of 40 in two large series, so the disease is neither rare nor necessarily symptomatic.[55] New or persistently localized pain, a fracture or a cortical erosion must be considered malignant until proven otherwise.

Neoplastic Lesions

Osteoid osteoma is considered by most authorities to be a benign neoplastic tumor and there is no evidence that malignancy occurs.[1]

Osteoblastoma, which is histologically similar[56] but larger than osteoid osteoma and with a different sex distribution,[5] has had only one reported sarcomatous transformation and with this tumor metastasis did not occur.[57]

Chondroblastoma may have a greater malignant potential than realized.[1] The reported cases of malignant chondromblastoma[58,59] showed no distinguishing histological characteristics to separate them from the usually benign form.[59] A chondrosarcoma developed 3½ years after curettage of a chondroblastoma and administration of 3,600 RADS of postoperative radiation.[60] This case had too short a latent period to fit the cri-

teria of Cahan for postradiation sarcoma of bone.[61] Others, however, have reported latent periods of less than five years.[62-64] It would seem best to exclude internally or externally irradiated patients from reports of spontaneous malignant transformation of a recognized benign tumor to a sarcoma.

Relatively few chondromyxoid fibromata are reported[8,9] and the malignant potential seems low.[9] Chondrosarcomatous transformation has been reported in a few cases.[65,66]

Treatment of Benign Tumors of Bone

In Table 3, treatment options are listed across the top and the "tumors" are arranged into groups based upon recommended treatment. Bloc excision must be understood to include amputation in an occasional case. The word expendable refers to the bone in which the tumor is located, and which can be partially or completely sacrificed without significant functional disability. In fact there are four bones that fit this definition: fibula, rib, clavicle and scapula. Portions of the spine and pelvis, if location is fortuitous, may also be resected with minimum disability. Major resections of pelvis or segmental resections of spine should ordinarily be reserved for truly malignant lesions, but may be required for extensive or recurrent benign lesions.

Lesions That Should Be Observed

Observation is recommended for osteochondromata unless persistent symptoms indicate serious interference with function or malignant conversion. Occasionally, cosmesis is a valid indication for excision. Irradiation is contraindicated because the cartilagenous tissue fails to respond and sarcomatous induction is possible.

Fibrous cortical defects and nonossifying fibroma should be expected to heal spontaneously without complication unless there is a latent pathological fracture, but nonossifying fibroma is less likely to heal and more likely to be the site of a fracture. Either lesion should be curetted and grafted if fracture is imminent.[1] If the lesion presents with a fracture, it should be expected that the fracture, but not necessarily the lesion, will heal.

Fibrous dysplasia should be generally observed, but curetted and grafted if pathologic fracture threatens.[1] Irradiation is contraindicated.[41]

Paget's disease should be closely observed. The pain is responsive to small doses of irradiation[54] and to various medications.[67] If pain is due to malignant degeneration, the prognosis is dismal.[51]

Lesions That Should Be Treated by Curettage and Graft

A unicameral bone cyst should be curetted and packed with graft unless it is in an expendable bone, which is unlikely.[68,69] If the cyst is small or near the epiphysis, observation alone may be acceptable if the diagnosis is histologically certain.[68] The recurrence rate of over 50 percent in the less than 10-year-old age group,[68,69] particularly in males,[69] has been noted in two large series. Chemical cauterization of the cavity is not helpful.[68] The type of graft material seems to be unimportant provided adequate packing of the cavity

TABLE 3.—*Management of Benign Bone Lesions*

"Tumor" Entity	*Observation*	*Curettage*	*Curettage-Graft*	*Bloc Excision*	*Cryotherapy*	*Irradiation*
Osteochondroma	Recommended	.....	.....	Enlarging, SX	.....	Not indicated
Fibrous defect	Recommended	.....	?Latent Fx	.....	.....	Not indicated
Fibrous dysplasia	Recommended	.....	Latent Fx	.....	.....	Contraindicated
Paget's disease*	Recommended	.....	.....	.....	.....	Effective (SX)
Solitary cyst	Active, small	.....	Recommended	?Expendable	.....	Contraindicated
Eosinophilic granuloma	NWB bone, HSC*	Acceptable	Recommended	.....	.....	Effective
Enchondroma	NWB bone, small	.....	Recommended	Expendable or recurrent	.....	Not indicated
Aneurysmal cyst	Contraindicated	.....	Recommended	Expendable or recurrent	?Recurrence	Inaccessible
Chondroblastoma	.....	.....	Recommended	?Expendable	.....	In adult?
Osteoblastoma	.....	.....	Recommended	Expendable	.....	Inaccessible
Chondromyx fibroma	.....	.....	.....	Recommended	.....	Unknown
Myositis ossificans	"Immature"	.....	.....	"Mature"	.....	Not indicated
Osteoid osteoma	Asymptomatic	Acceptable?	.....	Recommended	.....	Ineffective
Giant cell tumor	.....	.....	.....	Recommended	.....	Inaccessible

*May respond to drugs.

Fx = fractures
HSC = Hand-Schüller-Christian disease
NWB = bones not bearing weight
SX = symptoms

is achieved.[69] Irradiation is ineffective[1,5] and contraindicated because of damage to the epiphyseal plate in children and potential for subsequent sarcoma induction at any age.

The eosinophilic granuloma is also best treated with curettage and graft. If the lesion is in a bone not bearing weight, or is a second lesion of Hand-Schüller-Christian disease, simple observation is indicated. Radiation is effective at a dose of 300 to 600 RADS,[29] but the lesions heal without either surgical operation or radiation (the author has seen a massive lesion of the iliac bone heal completely following curettage alone). Prognosis for survival is excellent if only the skeleton is involved.[70]

Enchondroma is another lesion which is best treated by curettage and graft unless it is small and in a bone not bearing weight. In this event the lesion must be closely observed because of the possible misinterpretation of biopsy material which can resemble low grade chondrosarcoma. The reverse is also true.[1] The low recurrence rate following adequate surgical procedures and the low rate of malignant transformation of solitary enchondroma does not indicate bloc excision but this is an acceptable option in an expendable bone. Radiation is probably ineffective.[5]

The aneurysmal bone cyst can be massively destructive[17] and observation is contraindicated unless antecedent radiologic inactivity or regression is noted in the lesion. Medullary or cancellous lesions should be treated by curettage and graft although some lend themselves to local excisions.[1] Massive intraoperative blood loss can occur in these lesions. En bloc excision is quite acceptable in an expendable bone and can minimize bleeding. Cryotherapy has been successful.[16,71] Radiation might be used in treatment of the aneurysmal bone cyst in an inaccessible location and is reportedly successful at a dose between 2,000 and 3,000 RADS.[72]

Another lesion that is best managed by curettage and graft is benign chondroblastoma.[73-75] En bloc excision of an expendable bone or of a recurrence is acceptable.[1] Radiation is effective and acceptable after closure of the epiphyses[77] but the risk of sarcoma induction should be considered.[60]

Osteoblastoma should also generally be managed by curettage and graft, or possibly with bloc excision if located in an expendable bone. Radiation has occasionally been successful and is acceptable in inaccessible locations, or if surgical operation is refused or contraindicated.[5]

Lesions That Should Be Managed by Bloc Excision

It is recommended that chondromyxoid fibroma be managed by bloc excision as suggested by Spjut and co-workers,[1] Schjowicz,[9] Copeland[77] and Ralph.[78] The recurrence rate following curettage is as high as 25 percent[35] and there is evidence that this lesion has a slight malignant potential.[66] The effect of radiotherapy is unknown.[1]

The rather common but improperly named myositis ossificans[79,80] is classically managed by observation while it is "immature" and excision when "mature," if indications for surgical operation are present.[81] Exactly what constitutes immaturity and maturity and what surgical indications exist may be difficult to determine in a given case. Rest of the involved part in the early case is said to lead to absorption of the lesion,[81] but there is little evidence to support one particular course of management.

Symptomatic osteoid osteoma is best managed by bloc excision,[1] but curettage of the nidus may be acceptable in some locations provided removal is complete. These lesions may be self-limiting[82] and are occasionally asymptomatic.[83] Radiation is ineffective.[5]

Giant cell tumors are included in this list of benign tumors to emphasize that they may behave in a malignant manner and histologic grading correlates poorly with the prognosis.[13] Curettage results in recurrence in over half the cases and en bloc resection is strongly recommended.[84-86] Radiation is not always effective but perhaps is acceptable for inaccessible tumors.[13] In electing primary or supplemental radiotherapy there may be significant induction of a malignant giant cell tumor[14,87] and this type usually contains the more anaplastic lesions.[14]

Summary

Clinicians occasionally face the problem of optimum management of a bone lesion. Thorough clinical evaluation and careful radiographic study may allow diagnosis of lesions due to inflammatory, development, metastatic or metabolic processes. Even excluding these categories, there remains a large group of lesions which are listed in Table 1. These are related to their malignant counterparts in Table 2. Table 3 rearranges the most common of the benign tumors into groups for which a recommended plan is suggested, predicated of course upon reliable diagnosis. The

complexity and variability of histopathologic material makes interpretation difficult even in the hands of an experienced pathologist. Misdiagnosis is most often due to the failure to correlate all pertinent data in a tripartite discussion by clinician, radiologist and pathologist, as reemphasized most recently by Woods.[88]

The schema (Table 3) is presented as a guide but each lesion still requires individualization of management based upon age of the patient, location and extent of the tumor, consideration of the malignant potential, the surgeon's experience and capabilities, accessibility of supportive consultants and the patient's wishes. Treatment based upon overdiagnosis of the benign tumor or underdiagnosis of the malignant tumor is likely to result in a tragic outcome.

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Thromboembolic Problems

Identification of the high risk patient—the patient who is likely to have thromboembolic complications:

Surgical patients at greatest increased risk unfortunately are a large segment of our population. They are: patients over 40 years old with any type of heart disease—even well-compensated heart disease; those over the age of 50 with cancer; patients who are 20 percent or more over ideal weight; patients with ulcerative colitis; particularly those in whom major operative procedures in the lower abdomen have been done (this is more so than those having had upper abdominal work and more so than those having upper extremity or head and neck problems); women who have been on the pill and come in to the hospital even for minor procedures. (There are some very good data now out of England with ^{125}I fibrinogen showing an increased risk of about fourfold in that group. So, it's probably wise, when you can, to put these patients on some other form of contraceptive at least a month before the operative procedure.)

—WILLIAM W. COON, MD, *Ann Arbor*

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Argon Laser Management of Cutaneous Vascular Deformities

A Preliminary Report

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Twenty-two patients with cutaneous vascular malformations were treated with an argon laser. Promising results were obtained in patients with port-wine stains, hemangiomas, telangiectasia and varicose veins. The argon laser shows promise as an effective clinical tool in the treatment of all such cutaneous vascular abnormalities. However, further study of clinical as well as laboratory data is necessary over a long period of time before this modality can be definitely recommended as the treatment of choice for vascular deformities of the skin.

LASERS HAVE BEEN USED in medicine for a variety of surgical and nonsurgical problems for many years.[1-7] The Palo Alto Medical Clinic Department of Plastic and Reconstructive Surgery has been engaged in a pilot project investigating the use of argon lasers in the treatment of cutaneous vascular abnormalities. A study of 22 patients representing four major categories of lesions—port-wine hemangiomas, cavernous and capillary hemangiomas, telangiectasia and superficial varicose veins—has now been completed. Results in this group of patients were evaluated using clinical, photographic and biopsy studies. This new mode of treatment is as yet preliminary; however, results thus far appear to be encouraging. A second study group of 100 patients has been approved and is now in the process of being assembled.

From the Department of Plastic and Reconstructive Surgery, Palo Alto Medical Clinic.

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Discussion of Clinical Data

Twenty-two patients were treated at the Palo Alto Medical Clinic with an argon laser in a five-year study (Table 1). The diagnosis by category was port-wine hemangiomas, seven patients; varicose veins, nine patients; hemangiomas of the capillary or cavernous variety, two patients, and telangiectasia, four patients. Follow-up intervals have averaged 18 months for those with port-wine hemangiomas, 15 months for those with varicose veins, 10 months for those with capillary or cavernous hemangiomas and 13 months for the telangiectasia group. The average age of the patients with port-wine stains was 26.7 years; with hemangiomas, 25 years; with varicose veins, 40.9

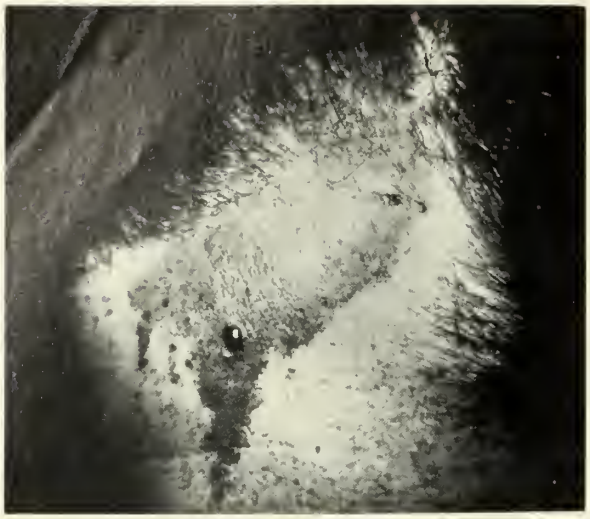

Figure 1.—Port-wine hemangioma of left upper forehead and hairline.

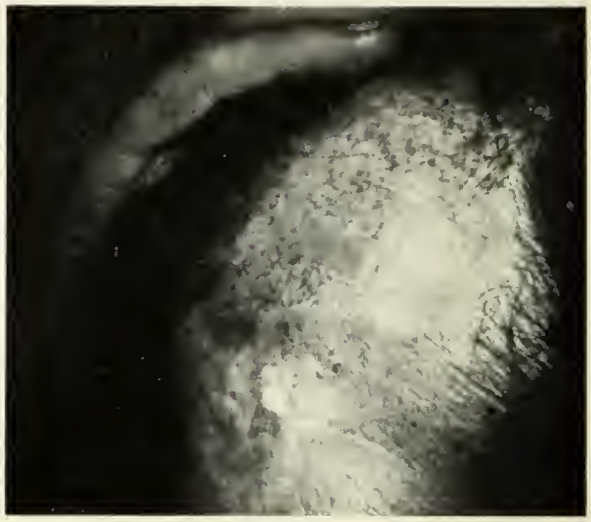

Figure 2.—Complete obliteration of majority of port-wine stain with no scarring.

years, and with telangiectasia, 35 years. There were very few associated diseases in any of the patients. Only the patients with varicose veins showed a family history correlated to the mother. It should be emphasized that the varicose vein group included those superficial varicosities that were found on the skin surface and were not the common greater and lesser saphenous varicose veins that are connected to the deep system. No patient had significant cardiorespiratory disease, was taking continuing medications or had significant allergies. The laser treatment power and dosage were correlated for each category and, remarkably, almost every category received approximately the same treatment regimen. Spot size averaged 1 mm, power averaged 1.5 watts (although later in the study, 1.8 watts was found to be the optimal dosage), time per exposure averaged 0.2 seconds. Only in the amount of exposures, that is the number of repetitive beams per time, were the categories notably different. The port-wine stain group received an average of 691 exposures per treatment correlating with the large size, mass and area of these lesions, and the desire of the patient and the physician to treat a greater percentage of the area during each laser treatment. The other categories received an average of 53 to 93 exposures per treatment.

TABLE 1.—*Summary of Data for 22 Patients Treated*

		Avg. Length Follow-up (months)	*Avg. Age (years)*	*Spot Size*	*Time (sec.)*	*Exposures*	*Power (watts)*
Port Wine	7	18	26.7	1 mm	.2	691	1.5
Varicose veins ..	9	15	40.9	1 mm	.2	93	1.5
Hemangioma ...	2	10	25	1 mm	.2	53	1.5
Telangiectasia ...	4	13	35	1 mm	.2	90	1.5

TABLE 2.—*Results of Argon Laser Treatment in 22 Patients*

		Excellent	*Good*	*Fair*	*No Change*	*Complications*
Port wine	7	4	3	..	..	.....
Varicose veins	9	..	..	1	8	2 minor scarring
Hemangioma	2	..	1	1	..	1 hypertrophic scar
Telangectasia	4	..	2	2	..	.....

Biopsy Findings

1. Nonspecific dermal fibrosis
2. Obliteration of small vessels
3. Sparing secondary skin appendages
4. Atrophy epidermis

Results

Complications and results (Table 2) were carefully evaluated by photographic, clinical and biopsy studies. There were only three complications or side effects in the entire series, and these were minimal. Two patients with varicose veins reported some very minor scarring which was not disfiguring. One patient in the hemangioma group underwent a hypertrophic change. Results have been evaluated and are divided into four categories: excellent, good, fair and no change. In the seven patients in the port-wine stain group, results were excellent in four and good in three (Figures 1 through 4). In the nine patients with varicose veins, there was a fair result in one, no significant change in six and no significant change but minor scarring in two. Later in the series as power was increased, satisfactory results were obtained in most of the varicose vein group (Figure 5). In the patients with telangiectasia there were two good results and two fair results. In the patients with hemangiomas, there was one good result and one fair result, the patient with the fair result having had the hypertrophic scar. Thus it appears that laser treatment is very promising for port-wine stains and of moderate-to-good effectiveness in treating telangiectasia, hemangiomas and varicose veins. Results of biopsy studies showed nonspecific subdermal fibrosis, obliteration of small vessels and sparing of secondary skin appendages, with mild atrophy of the epidermis.

Figure 3.—Typical port-wine stain of left forehead, eyelids, cheek, nose and upper lip.

Figure 4.—Complete obliteration of forehead area of stain without scars. Remainder of face is under treatment at present.

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Figure 5.—Ankle and Achilles tendon area is untreated and posterior calf has been treated with complete obliteration of superficial network of varicose veins similar to those present on ankle.

Medical
PROGRESS

Refer to: Moss AJ, Gussoni CC, Isabel-Jones J: Echocardiography in congenital heart disease (Medical Progress). West J Med 124:102-121, Feb 1976

Echocardiography in Congenital Heart Disease

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ECHOCARDIOGRAPHY, introduced more than two decades ago,[1] is now considered an established procedure of paramount importance in cardiac diagnosis. Initial interest in its application centered mainly on acquired heart disease with particular emphasis on mitral stenosis,[2-29] pericardial effusion[2,6,8,10,17-20,30-41] and atrial tumors.[8,17,18,20,42-44] Although use of ultrasound in the diagnosis of congenital heart disease was first reported as early as 1958,[45] it was not until recently that sufficient data became available to permit its use as a practical tool in pediatric cardiology.

The first important reference to echocardiography in congenital heart disease was made by Ultan and co-workers in 1967.[46] These authors published preliminary observations on tricuspid and mitral valve motion in patients with cardiac shunts and also described criteria for the echocardiographic identification of subaortic membranous obstruction. In 1969, Popp and associates identified two different patterns of septal motion in atrial septal defect.[47] By the early 1970's, the echocardiographic features for recognition of a wide variety of specific lesions had been reported.[48-64] Publication of normal values for the different echocardiographic measurements in the pediatric age group[55,57,59,65-73] provided the means for further progress in this area. Diagnostic ultrasound in infants and children has found particular favor because of its noninvasive nature and presumed safety.[73-77]

This review is concerned only with the single crystal method of conventional echocardiography. The multiple crystal,[78-80] the real-time-two-dimensional[81] and the B-scan systems[82-85] are not considered because of their current embryonic stage of development. However, it appears at this time that these newer applications of cardiac ultrasound have great potential for use in congenital heart disease, since they permit precise definition of cardiac anatomical interrelationships and valvular motion.

Principles of Echocardiography

Echocardiography[86,87] utilizes the principle of pulsed reflected ultrasound in frequency range of 1 to 10 mHz (mega-Hertz = millions of cycles per second), most commonly 2.25 to 5 mHz. Frequency is inversely related to wave length; thus, the higher the frequency the smaller the wave length. Frequency is, therefore, an important consideration in selecting the appropriate size transducer for patients of different sizes and with different chest contour.

As the ultrasound beam transmitted from the transducer passes through a homogeneous medium, its path is a straight line. However, when it passes through the interface of two media with different acoustic impedances, the beam is reflected or refracted or both. The amount of reflection depends not only on the differences in acous-

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ABBREVIATIONS USED IN TEXT

ARD = aortic root diameter
AVO = aortic valve opening
IHSS = idiopathic hypertrophic subaortic stenosis
IST = interventricular septal thickness
LAD = left atrial dimension
LVD = left ventricular dimension
LVPW = left ventricular posterior wall
MVCF = mean velocity circumferential fiber shortening
MVDE = mitral valve diastolic excursion
MVTE = mitral valve total excursion
MVVS = mitral valve velocity slope
RVD = right ventricular dimension
TVVS = tricuspid valve velocity slope

tic impedance but also on the angle of incidence. As the ultrasound beam approaches being perpendicular to the interface, most of the sound is reflected. Reflection is also dependent upon the size of the wave length relative to the object at the interface. A smaller wave length (that is, higher frequency) can reflect sound waves from smaller objects and also can distinguish objects which are close together. Thus, the higher frequency transducers are best used in small infants.

The reflected sound waves returning to the transducer are converted to an electrical signal which can be displayed on an oscilloscope.

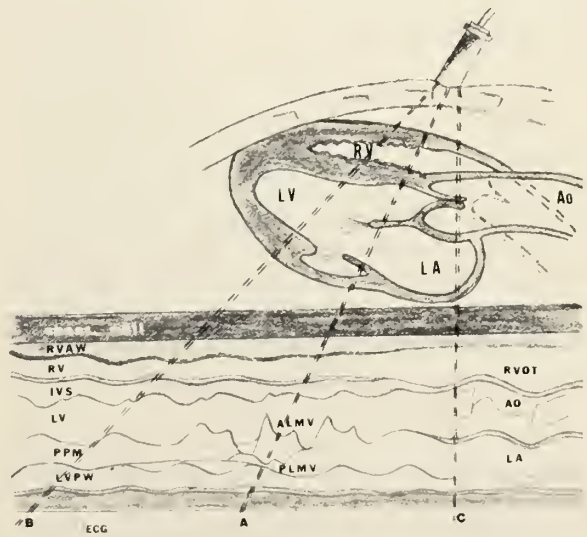
Registration of Echocardiograms in Infants and Children

Important differences exist between echocardiography in adult and in pediatric patients and it is essential that the operator be aware of these.

The Apparatus—In small infants, a high frequency transducer is recommended since this permits better resolution and less dispersion of the beam. The loss of penetration which occurs with higher frequency does not usually present a problem because the dimensions of an infant chest are small. In older children, an adult transducer may be used (2.25 mega-Hertz frequency and 0.5 to 0.75 inch diameter).[64,88,89] In neonates, a 5 mega-Hertz, 0.25 inch diameter, nonfocused transducer has been shown to give the best results,[69,72,89] although transducers with frequency from 2.25 to 9 mHz have been used in infants. The smaller diameter of the transducer in a small infant is more likely to allow an airless contact with the skin.

As with adults, an electrocardiogram must be recorded simultaneously with the echocardiogram so that the movements of the echo signals can be related to the cardiac cycle. Other measurements such as a phonocardiogram may be useful in distinguishing the pulmonic from the aortic valve by temporal correlation with the second sound. This may be particularly important in such lesions as d-transposition of the great arteries. Simultaneous registration of the carotid arterial pulse has had little application in pediatrics owing to technical difficulties encountered in infants.

Because of the complex nature of many of the congenital cardiac anomalies, it is preferable to record the echoes on a strip-chart recorder. This permits not only identification of the various cardiac structures but also their relationship with one another. For example, lack of continuity of the mitral valve and aortic root, best shown by strip-chart recorder, is crucial to the diagnosis of double-outlet right ventricle. Also, the relationship of the semilunar and atrioventricular valves may form the basis for echocardiographic recognition of ventricular inversion.



ALMV = anterior leaflet of mitral valve
AO = aorta
IVS = interventricular septum
LA = left atrium
LV = left ventricle
LVPW = left ventricular posterior wall
PLMV = posterior leaflet of mitral valve
PPM = posterior papillary muscle
RV = right ventricle
RVAW = right ventricular anterior wall
RVOT = right ventricular outflow tract

Figure 1.—Schematic illustration of longitudinal section of the heart showing transducer positions on the chest, directions of ultrasound beams through the heart and the corresponding echotraces. Position A is through the mitral valve region, position B is through the ventricular region and position C is through the root structures.

TABLE 1.—*Echocardiographic Values in Normal Newborns*

	Hagan, et al[69] 10-72 hr 2.7-4.5 kg	*Mayer, Kaplan*[59] 5-125 hr 2.3-4.9 kg	*Solinger, et al*[70] 1½-192 hr 2.2-4.5 kg	*Godman, et al*[71] 6 hr-4 wk 1.9-4.3 kg	*Lundstrom*[55] 1 wk-1 mo ?	*Winsberg*[67] 12-120 hr 2.8-4.5 kg	*Sahn, et al*[72] 12-120 hr 2.7-4.5 kg	*All Cases** 1½ hr-1 mo 1.9-4.9 kg	
No. of cases	(200)	(50)	(240)	(50)	(10)	(11)	(72)	(633)	
MVD	....	31-47	22-32	....	....	....	....	(290)	22-47mm
MVTE	....	6-12	8.5-13.1	6.5-12.4	10-14	....	....	(300)	6.5-14mm
MVDE	6-12		....	....	7-9	....	....	(210)	6-12mm
MVVS	60-130	36-80	....	....	....	....	....	(250)	36-130mm/sec
TVD	....	24-32	13-19	....	....	....	....	(290)	13-32mm
TVTE	....	8-14	8.8-14.2	8-13	12	....	....	(300)	8-14.2mm
TVDE	7-14		....	....	....	....	....	(200)	7-14mm
TVVS	60-116	34-56	....	....	....	....	....	(250)	34-116mm/sec
ARD	8.1-12	7-12(S)	9.3-13.6(S)	8-11(S)	....	....	....	(540)	7-13.6mm
AVO	....	....	4-6.8	....	....	....	....	(240)	4-6.8mm
PRD	9.4-13	....	10.7-15.8(S)	9.2-12.8(S)	....	....	....	(490)	9.2-15.8mm
PVO	....	....	5.8-9.9	....	....	....	....	(240)	5.8-9.9mm
LAD	5-10	6-13(S)	6.8-13.5(S)	4-10.5(S)	....	....	....	(540)	4-13.5mm
IST	1.8-4	....	2.1-4.5(D)	....	....	....	....	(440)	1.8-4.5mm
LVPW(S)	2.5-6	....	....	....	....	6	....	(200)	2.5-6mm
LVPW(D)	1.6-3.7	....	2-4.6	....	....		....	(440)	1.6-4.6mm
LVD(S)	8-18.6	....	....	....	....	8-12	....	(211)	8-18.6mm
LVD(D)	12-23.3	12-20	16.1-24.1	12-20.4	....	16-20	....	(351)	12-24.1mm
RVAW(S)	3.3-7.3	....	....	....	....	....	....	(200)	3.3-7.3mm
RVAW(D)	2-4.7	....	1.1-4.1	....	....	....	....	(440)	1.1-4.7mm
RVD(S)	5.5-11.4	....	....	....	....	....	....	(200)	5.5-11.4mm
RVD(D)	6.1-15	10-17	10.4-17.7	10-17.5	....	....	....	(540)	6.1-17.7mm
MVCF	....	....	....	....	....	....	0.92-2.2	(72)	0.92-2.2circ/sec
SV	....	....	....	....	....	2.76-6.27	....	(11)	2.76-6.27ml

MVD = mitral valve depth
MVTE = mitral valve total excursion
MVDE = mitral valve diastolic excursion
MVVS = mitral valve velocity slope
TVD = tricuspid valve depth
TVTE = tricuspid valve total excursion
TVDE = tricuspid valve diastolic excursion
TVVS = tricuspid valve velocity slope
ARD = aortic root diameter
AVO = aortic valve opening
PRD = pulmonary root diameter
PVO = pulmonary valve opening
LAD = left atrial dimension
IST = interventricular septal thickness
LVPW = left ventricular posterior wall
LVD = left ventricular dimension
RVAW = right ventricular anterior wall
RVD = right ventricular dimension
MVCF = mean velocity circumferential fiber shortening
SV = stroke volume
(S) = systole
(D) = diastole

*Figures in parenthesis = number of cases.

The Patient—Proper registration of the echocardiogram requires cooperation of the patient. Infants and young children often will not cooperate, and physical restraint to prevent movement usually results in vigorous crying. With tenderness and patience (and sometimes with the help of a pacifier)[59,69] a satisfactory recording can usually be obtained. Rarely, one must use sedation.[84,85,88] In the case of a neonate, care must be taken to maintain an even body temperature and also to maintain the head in the mid-line position to prevent rotation of the heart.[70] The study can be easily carried out with the infant in an incubator or bassinet.

Technical Considerations—Because of the wide variety of complex congenital cardiac anomalies, it is important that the operator be made aware of the differential diagnosis in each patient. This is particularly important in cases of malposition of the heart.

Contrary to the experience in adults, echoes from most cardiac structures can be satisfactorily recorded with the subject in the supine position only.[69-72,89] Also, the smaller amount of extracardiac thoracic tissue in infants and young children interferes less with the cardiac echoes than in adults.[69,88] In a neonate, echoes from the tricuspid valve can be recorded with the transducer positioned directly *on* the sternum (which at this age is cartilaginous, allowing penetration of the ultrasound beam) at the level of the third interspace.[70] This cannot be done in adults or in older children.

Since congenital heart lesions sometimes involve malposition of cardiac structures, it is essential that the interpreter of an echocardiogram know the position of the transducer and the direction of the beam.

The Normal Echocardiogram

Attempts should be made to record echoes from all areas of the heart. This is usually best accomplished by first locating the mitral valve and then sweeping the transducer over the left ventricular region and over the region of the root structures (Figure 1). Echocardiographic values

in normal infants and children are shown in Tables 1 through 3.

Mitral Valve Region (Figure 2)—The mitral valve echoes are recorded by placing the transducer in the third or fourth intercostal space at the left sternal border and directing the beam posteromedially. In this position, the beam traverses the anterior chest wall, the anterior wall of the right ventricle, the right ventricle, the interventricular septum, the left ventricle, the anterior mitral leaflet and the posterior wall of the left atrium or left ventricle in that order. Early in ventricular systole, the mitral valve trace falls posteriorly from point B to point C as the leaflet moves toward the left atrium. During the remainder of systole, the curve gradually moves anteriorly from C to D as the ventricle empties. This anterior movement represents displacement of the mitral ring with ventricular contraction rather than opening of the anterior leaflet. In early diastole, the echotrace rises abruptly to a peak (E) as the leaflet opens into the left ventricle. A steep fall follows this peak, and the curve moves posteriorly from E to F as the leaflet floats back toward the left atrium. In late diastole, the echotrace again shows an anterior movement to

TABLE 2.—*Echocardiographic Values in Normal Children Based on Body Weight*

	Weight (kg)	*Feigenbaum*[66] *(mm)*	*Lundstrom*[73] *(mm)*
RVD(D)	11	3-15	4-11
	12-22	4-15	4-11
	23-34	7-18	4-11
	35-45	7-16	4-11
	46-56	8-17	4-11
	57-90	12-17	....
LVD(D)	11	13-32	12-31
	12-22	24-38	22-37
	23-34	33-45	28-42
	35-45	35-47	33-46
	46-56	37-49	37-49
	57-90	44-52	....
IST(D) LVPW(D)	11	4-6	3-5
	12-22	5-7	4-6
	23-34	6-7	5-7
	35-45	7-8	5-7
	46-56	7-8	5-7
	57-90	7-8	....
LAD(S)	11	7-23	7-22
	12-22	17-27	15-27
	23-34	19-28	19-30
	35-45	20-30	24-33
	46-56	21-30	26-35
	57-90	21-37	....
ARD(D)	11	7-17	8-19
	12-22	13-22	14-24
	23-34	17-23	19-26
	35-45	19-27	21-29
	46-56	17-27	23-31
	57-90	22-28	....
AVO(S)	11	5-12	....
	12-22	9-16	....
	23-34	12-17	....
	35-45	13-19	....
	46-56	14-20	....
	57-90	16-20	....

For abbreviations—see Table 1

TABLE 3.—*Echocardiographic Values in Normal Children Based on Body Surface Area*

	BSA (M²)	*Feigenbaum*[66]	*Tajik, et al*[67]	*Lundstrom, Edler*[68]
MVTE	1	....	10-23	....
	1	....	....	....
MVVS	1	....	70-160	90-130*
	1	....	....	90-180†
TVVS‡	.	....	....	55-160
ARD(D)	1	7-22	....	....
	1	17-28	....	....
AVO(S)	1	5-16	....	....
	1	13-20	....	....
LAD(S)	1	7-28	....	....
	1	20-37	....	....
IVT(D)	1	4-7	....	....
LVPW(D)	1	6-8	....	....
LVD(D)	1	13-42	....	....
	1	33-52	....	....
RVD(D)	1	3-18	4-14	....
	1	7-17	7-14	....
RVI	1	....	5-13	....
	1	....	5-11	....

BSA = body surface area
RVI = right ventricular index in mm/M². All other echocardiographic values in mm
For additional abbreviations—see Table 1

*Less than 0.5M².
†Greater than 0.5M²
‡Not related to BSA.

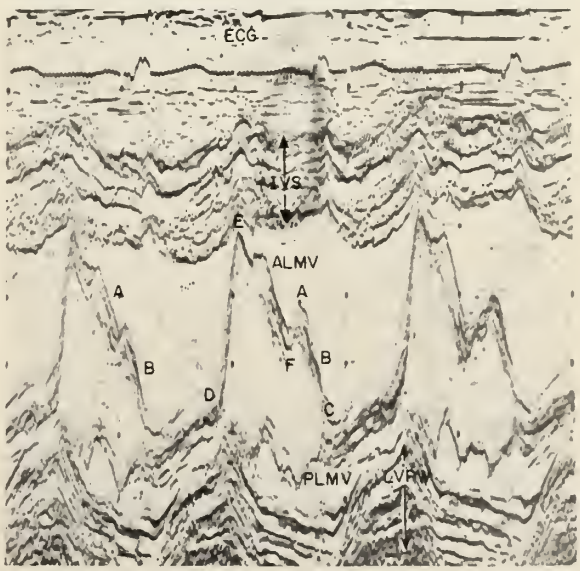


Figure 2.—Echocardiogram of mitral valve as would be recorded from Position A of Figure 1. Both the anterior and posterior leaflets of the valve are shown Points A-F are described in the text. (See Figure 1 for abbreviations.)

point A following contraction of the left atrium. With closure of the leaflet, the curve moves posteriorly from point A to point B.

Point E represents the maximal opening of the mitral leaflets in early diastole and coincides with the opening snap in mitral stenosis. The peak of the A wave represents the opening of the mitral leaflet induced by atrial contraction and coincides with the fourth heart sound. Point C represents the closed position of the anterior mitral leaflet in early systole and coincides with the first component of the first heart sound. The posterior leaflet moves in the opposite direction to the anterior leaflet, and the excursions are not so pronounced.

The anterior leaflet of the mitral valve can be shown to be continuous with the posterior wall of the aortic root, and assessment of this relationship can be made by rotation of the sonic beam from the anterior mitral valve leaflet to the aortic root by a rapid medial and superior movement of the transducer.

A number of measurements are made from the mitral valve area. Mitral valve depth (MVD) is the distance from the chest wall to the most anterior point of the mitral valve (E point). Mitral valve total excursion (MVTE) is measured perpendicularly from point E to a line drawn between the preceding and following C points. Mitral valve diastolic excursion (MVDE) is measured perpendicularly from point E to a line drawn between the preceding and following D points. The distance from the E point to a corresponding point on the posterior leaflet represents the orifice size relative to mitral flow. No values for this measurement have been reported. The closing mitral valve velocity slope (MVVS), represents the third side of a right angle triangle in which the base is one second in time and the hypotenuse is a continuation of the E to F slope (Figure 3). The E-F slope represents the closing velocity of the anterior mitral leaflet. This slope is diminished with mitral stenosis, with decreased left ventricular compliance and other conditions in which there is a reduced rate of mitral flow.

All of the above measurements should be made in the region of maximal excursion of the mitral valve.

Ventricular Region (Figure 4)—With move-

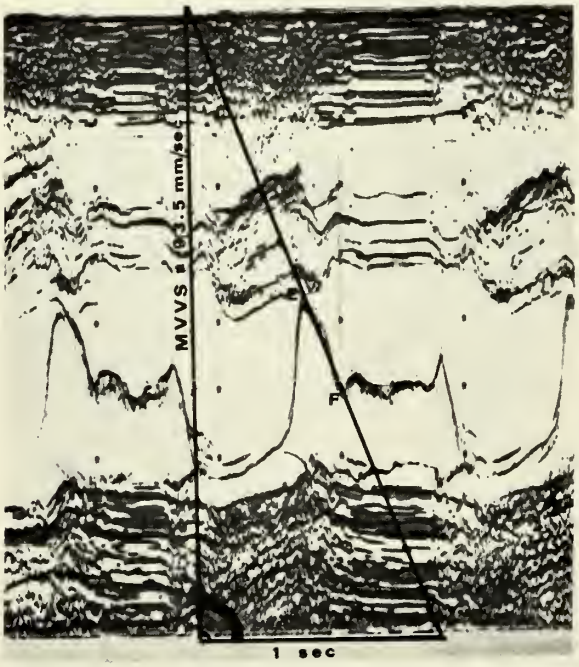


Figure 3.—Echocardiogram of mitral valve showing the closing mitral valve velocity slope (MVVS). When this slope is not single as in the preceding figure, the initial deflection should be considered as the E point.

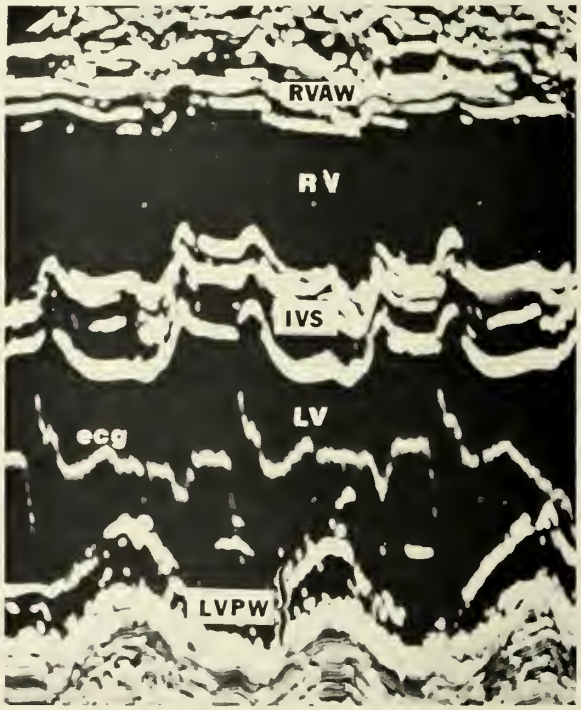


Figure 4.—Echocardiogram of ventricular region which was obtained from Position B (Figure 1) of the transducer. Specific points of measurement are not illustrated. Some authors prefer to measure right ventricle (RV) and left ventricle (LV) diastolic dimension at the peak of the R wave, while others at the beginning of the QRS complex. Similarly, some measure RV and LV systolic dimension at the maximum point of posterior wall excursion, others at the maximum point of septal excursion, and still others at the smallest systolic diameter. (See Figure 1 for abbreviations.)

ment of the beam inferiorly and laterally, echoes may be recorded below the mitral valve area from the right ventricle, interventricular septum and the left ventricle. Right ventricular anterior wall (RVAW) is measured at both end-systole and end-diastole from epicardium to endocardium. Right ventricular dimension (RVD) is the internal measurement of the right ventricular cavity both at end-systole and end-diastole. The interventricular septal motion is normally opposite to that of the left ventricular posterior wall, that is, anterior in diastole and posterior in systole. Paradoxical movement (motion parallel to the posterior wall motion) in the upper third of the septum is normal.[47,69,91] However, paradoxical motion in the lower two thirds of the septum is abnormal and may imply right ventricular volume overload. Two different patterns of abnormal septal motion associated with right ventricular volume overload have been described.[91] These are complete reversal (paradoxical septal motion) of the normal pattern (Type A) and flattening of the septal echoes in systole with little motion during diastole (Type B). Interventricular septal thickness (IST) is measured at the end of diastole and at the end of systole. Left ventricular posterior wall (LVPW) and left ventricular dimension (LVD) measurements are made in the same manner as described for the right ventricle.

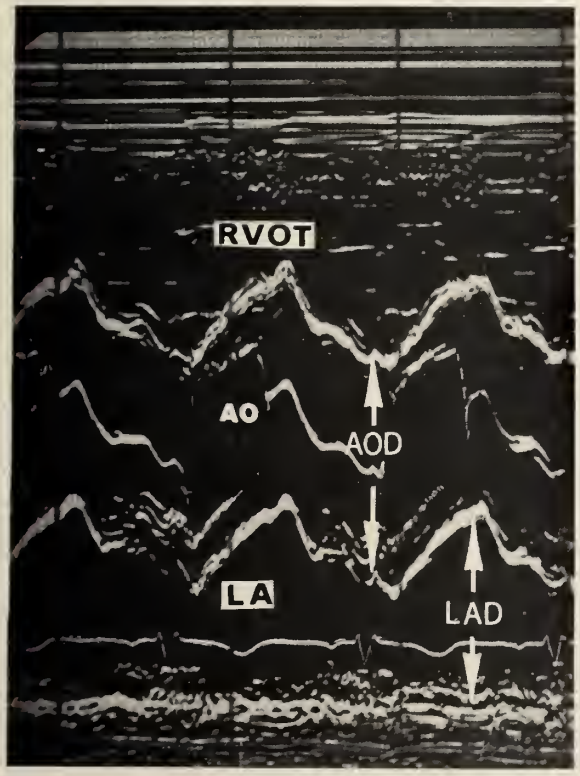


Figure 5.—Normal echocardiogram of root structures. Echotrace of the aortic valve in systole and diastole, right ventricular outflow tract (RVOT) and left atrium (LA) are shown. Arrows illustrate the points of measurement for aortic root diameter (AOD) and left atrial dimension (LAD). In this illustration the points of measurements are as described by Brown and associates.[94] However, other studies suggest AOD at end-systole, from outside diameter, or internal diameter.[69,70,73]

In neonates, all of the above measurements are made in the region of the mitral valve because, in this age category, the mitral valve is more inferior.[72]

Root Structures (Figure 5)—The echo pattern of the aortic root is recorded by locating the mitral valve echo and then directing the transducer medially and superiorly toward the right shoulder. The aortic root and valve may also be recorded directly with the transducer placed at the second or third intercostal space just to the left of the sternum and directed slightly medially and superiorly.[55,70] The pattern consists of two parallel signals moving together anteriorly during systole and posteriorly during diastole. The echotraces of the aortic valve can be visualized within the lumen of the aortic root. The posterior margin of the aortic root is continuous with the anterior leaflet of the mitral valve, and the anterior margin is continuous with the interventricular septum (Figure 1). Measurement of the aortic root diameter (ARD) at the outside diameter in end systole has been recommended for infants and children.[70,73] Recently, the end diastolic dimension has been recommended to avoid variations which may be seen during systole.[93,94] Hagan and coworkers, however, found the difference between end systolic and end diastolic diameters of both great arteries was less than 1 mm.[69] Aortic valve opening (AVO) is the maximal distance between the cusps in systole. Two cusps are usually visualized. The anterior is the right coronary cusp and the posterior is probably the noncoronary cusp.[95] Occasionally the third cusp, the left coronary cusp, is seen in systole in the midline in that it moves laterally and maintains a position parallel to the aortic wall.[93]

The echo-free space anterior to the aortic root corresponds to the right ventricular outflow tract, and the echo-free space posterior to the aortic root, to the left atrium. The posterior wall of the left atrium can be identified by its posterior motion during systole. The left atrial dimension (LAD) is the internal dimension from the posterior wall

of the aorta to the endocardium of the left atrial wall. This measurement is made in end systole.

The pulmonary valve area is easier to visualize in young children than in adults. The transducer is placed at the first or second left parasternal space and directed toward the left shoulder. In neonates, it can be detected by placing the transducer in the second left interspace and directing it inferiorly.[70] It can also be detected in neonates by positioning the tranducer in the third left parasternal space and directing it laterally.[69] The pulmonary root diameter (PRD) and pulmonary valve opening (PVO) measurements are obtained as described for the aorta. A thick band of echoes seen posterior to the pulmonary artery probably represents the crista supraventricularis.[62]

Other Measurements—The tricuspid valve is visualized by angulation of the transducer inferomedially from the position used for locating the aortic valve. In neonates, echoes from this structure may be recorded with the transducer over the left half of the sternum at the level of the third intercostal space without angulation.[70] Its pattern of motion is the same as that of the mitral valve. Diameter and excursion measurements of this valve are more easily obtainable in neonates than in infants and older children.

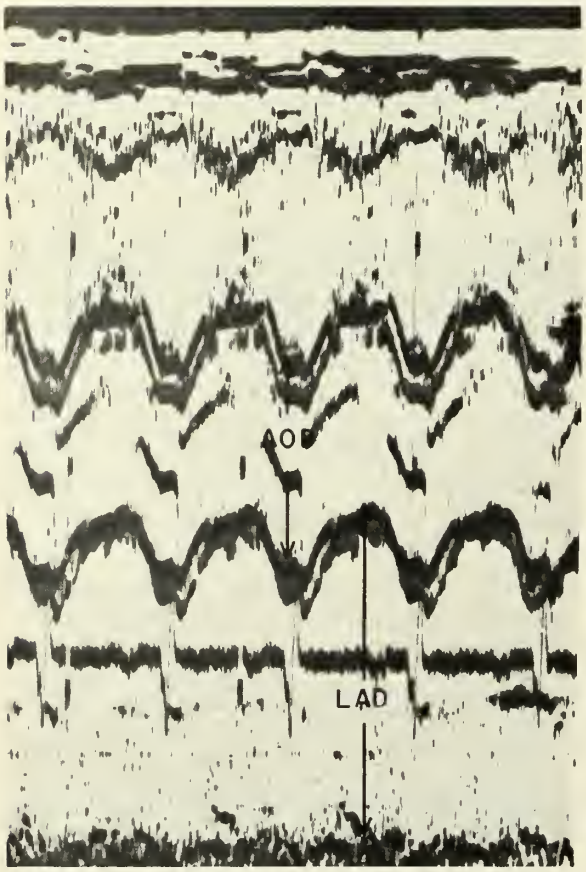


Figure 6.—Echocardiogram in newborn infant with patent ductus arteriosus. Dimension of left atrium (LA) is increased. It should be noted also that the dimension of the left atrial cavity is considerably greater than the aortic root (AO), (LAD/AOD = 1.6).

Considerable attention has recently been directed toward the echocardiographic estimation of left ventricular volume and function in adults. Recently Meyer and co-workers have shown that parameters of left ventricular performance in children with congenital heart disease can be reliably measured by echocardiography.[97] Sahn and associates[72] reported values for the normal mean velocity of circumferential fiber shortening (MVCF)* and Winsberg and co-workers[67] reported values for the normal stroke volume (SV)† of the left ventricle. The validity of ventricular volume estimated by echocardiography remains controversial in that the accuracy is dependent upon the size and shape of the ventricle and, therefore, the underlying lesions.

Specific Lesions

Ventricular Septal Defect‡—There are no diagnostic features in echocardiograms. With very large defects, a portion of the septum may disappear as the ultrasonic beam sweeps from the apex to the root of the aorta. A linear relationship has been shown between LAD and the magnitude of the left-to-right shunt.[73,100,101] Right ventricular dimension (RVD), pulmonary root diameter (PRD), left atrial dimension (LAD), mitral valve velocity slope (MVVS) and left ventricular dimension (LVD) may be increased as a result of the left-to-right shunt with resulting increased pulmonary, left atrial, mitral and left ventricular flow.

Patent Ductus Arteriosus (Figure 6)§—There are no diagnostic echocardiographic features. As may be expected with significant left-to-right shunting and left heart volume overload the aortic root diameter (ARD), pulmonary root diameter (PRD), left atrial dimension (LAD) and left ventricular dimension (LVD) may be increased. An increase in MVVS and MVCF shortening has been described.[46,100,101] Serial echocardiography to evaluate increasing LAD and LVD may be useful to assess the course of infants with respiratory distress syndrome complicated by patent ductus ar-

$$*\text{MVCF/second} = \frac{\text{LVD (diastole)} - \text{LVD (systole)}}{\text{LVD (diastole)} \times \text{ejection time}}$$

†SV (ml) = LVD (diastole)^3 − LVD (systole)^3

‡References 46,66,73,95-101

§References 46,65,73,99-101,103-106

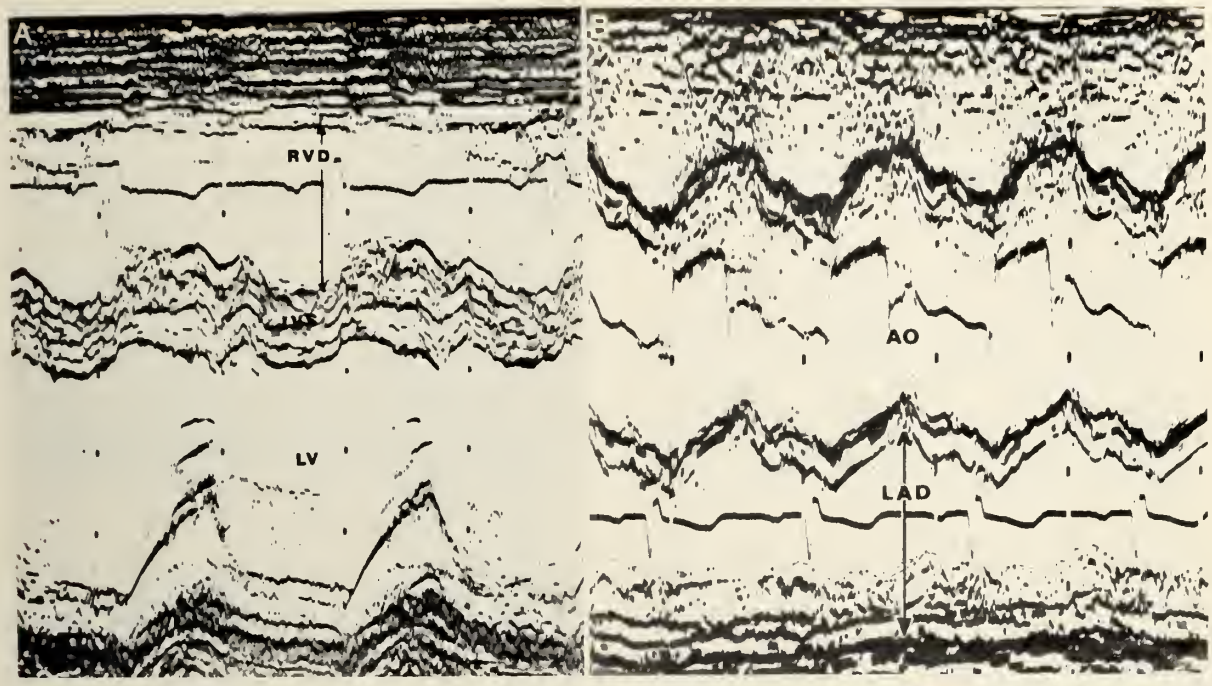


Figure 7.—Echocardiogram in 14-year-old girl with atrial septal defect. **A**, note abnormal motion (Type B) of interventricular septum (IVS) and the increased right ventricular dimension (RVD). The actual measurement was 20 mm which is considered increased for this age child. (LV=left ventricle). **B**, the left atrial dimension (LAD) measured 14 mm which is smaller than normal for this age and size. (AO=aortic root).

teriosus.[104] LAD to ARD ratio has also been used for this purpose.[73,105,106]

Atrial Septal Defect (Figure 7)*—The two significant criteria for echocardiographic recognition are increased RVD and abnormal septal motion. The two different patterns of abnormal septal motion have been previously described—Type A and Type B.[47] The greater stroke volume of the right ventricle is believed to be responsible for the abnormal septal motion, and this hypothesis is compatible with the observation that identical motion may be observed in anomalous pulmonary venous return. It probably represents right ventricular overload, since it also occurs in pulmonic and tricuspid insufficiency. The fact that abnormal septal motion is not always reversible with surgical correction suggests that other factors may also be operative. With pulmonary hypertension (elevated pulmonary vascular resistance) or with associated left ventricular overload, septal motion in right ventricular overload lesions may remain normal.[52,71,99,114] It is important to recognize that abnormal septal motion with defects associated with right ventricular overload may not be observed in the early days of life.

In some cases a systolic hump in the mitral echo, similar to the abnormal motion in idiopathic

*References 13,46,47,52,57,66,73,88,99,107-116

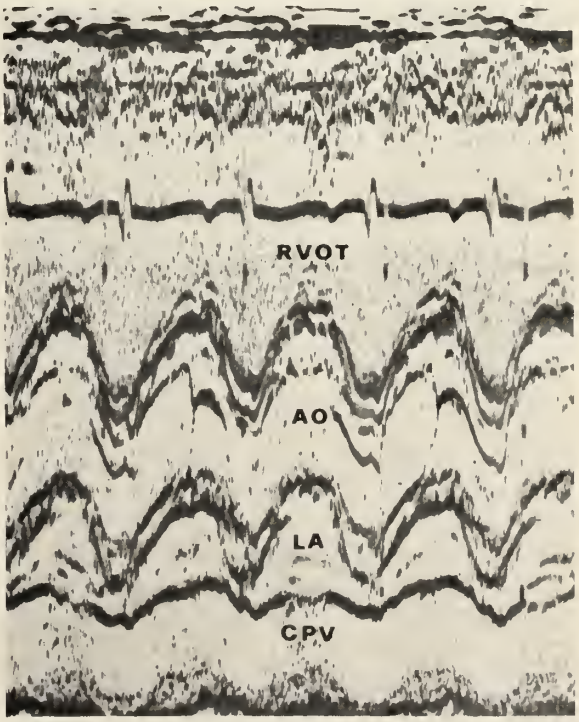


Figure 8.—Echocardiogram of 1-month-old infant with total anomalous pulmonary venous return. Note echo-free space behind posterior wall of left atrium representing the common pulmonary vein (CPV). The dimension of the left atrium (LA) is reduced in comparison with that of the aorta (AO). (RVOT=right ventricular outflow tract.)

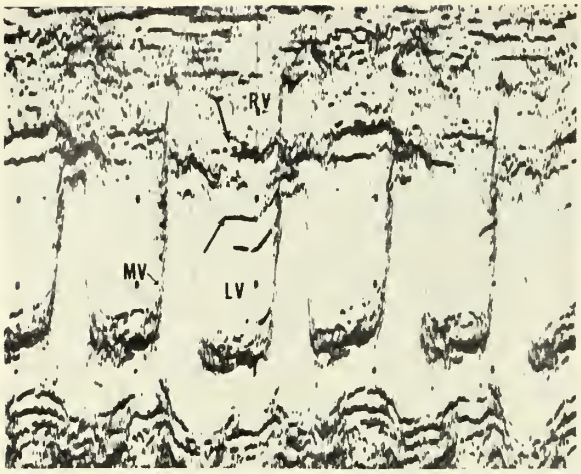


Figure 9.—Echocardiogram in 1-year-old infant with endocardial cushion defect. Note exaggerated excursion of anterior leaflet of mitral valve (MV) with movement from a posterior position in left ventricular (LV) during systole to an anterior position through ventricular septum into right ventricle (RV) during diastole. The gain setting permitted registration of only remnants of the ventricular septum (arrows).

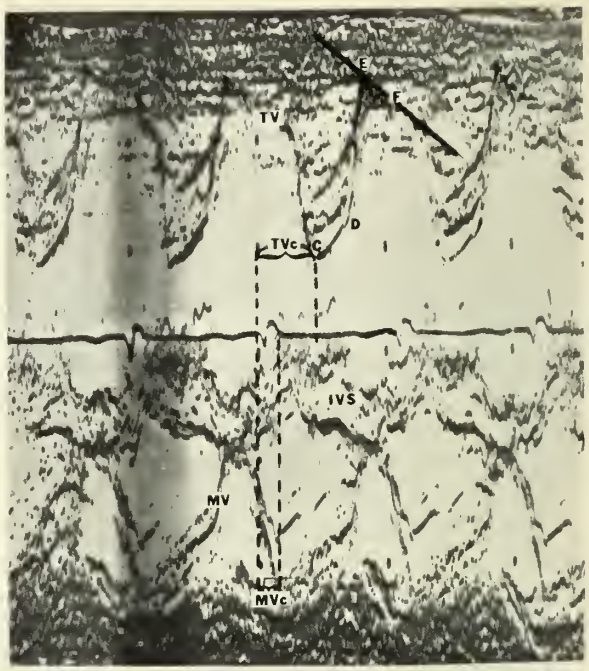


Figure 10.—Echocardiogram in 3-year-old child with Ebstein's anomaly. Right ventricular dimension is increased for age, tricuspid valve (TV) slope is diminished, in comparison to the mitral valve (MV) slope, and tricuspid valve closure (TVc) is delayed. Excursion of tricuspid valve is increased in comparison with mitral valve. Abnormal motion of ventricular septum usually observed in this abnormality is not seen. (MVc = mitral valve closure.)

hypertrophic subaortic stenosis (IHSS), is observed.[50,54,117] The velocity, slope and amplitude of diastolic excursion of the mitral valve (D-E) have been described as reduced, particularly as they apply to the posterior leaflet.[116] These measurements are more specifically a reflection of mitral valve flow. The TVVS may be increased.

Anomalous Pulmonary Venous Return (Figure 8)*—The echocardiographic features are the same as for atrial septal defect except for the following: (1) The mitral valve echo is normal in configuration and velocity although the amplitude may be diminished, dependent upon mitral valve flow. (2) There may be an echo-free space behind the posterior wall of the left atrium, presumably representing the common pulmonary vein.[118] (3) LAD and LVD are reduced.

In a newborn with high pulmonary vascular resistance or when pulmonary vascular obstruction is present, paradoxical motion of the ventricular septum may not be seen.[71,99]

Endocardial Cushion Defect (Figure 9)†—The echocardiographic features of ostium primum defect are as follows: (1) Abnormal septal motion when mitral regurgitation is mild or moderate, (2) narrowing of left ventricular outflow tract, (3) prolonged approximation of anterior mitral leaflet to the ventricular septum during diastole, (4) occasional systolic anterior motion of the mitral valve (this differs from the movement of the anterior leaflet of the mitral valve in IHSS in that the motion is more gradual and there is no posterior component of that motion in endocardial cushion defect) and (5) a double echo representing the two edges of the mitral cleft recorded from the anterior leaflet.

In complete atrioventricular canal, the septal motion is normal and with sweeping of the transducer, the ventricular septal defect may become apparent. Also, the anterior leaflet of the mitral valve progressively assumes a more anterior position with superior sweeping of the transducer, eventually joining the anterior wall of the aortic root. A number of different movements of the common valve have been described according to their anatomy: (1) exaggerated excursion of the anterior mitral leaflet with movement from a posterior position in the left ventricle during systole to an anterior position *through* the ventricular septum into the right ventricle during diastole (free-floating common atrioventricular leaflet), (2) giant excursion of the mitral component with reduced excursion of the tricuspid component and

*References 56,71,73,97,107,114,115,118
†References 46,54,57,65,92,97,98,119,120

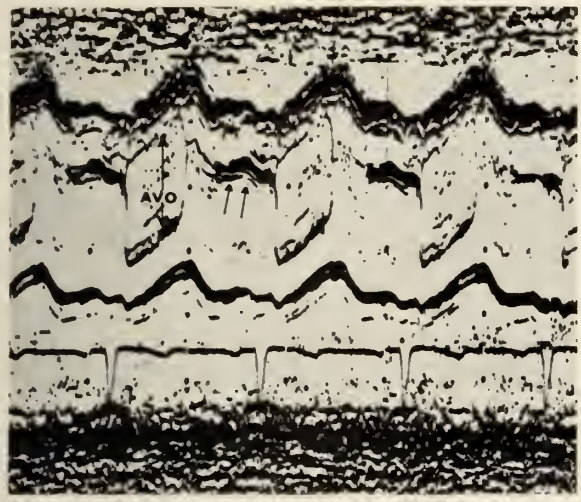


Figure 11.—Echocardiogram of 7-year-old child with valvular aortic stenosis. Aortic valve opening (AVO) is reduced for age. Multiple echoes of aortic valve seen in this condition are also observed (arrows). The valve is also eccentric in diastole suggesting bicuspid aortic valve.

vice versa, (3) double contour of the mitral valve in diastole and (4) prolonged approximation of the mitral valve to the ventricular septum during diastole.

Ebstein's Anomaly (Figure 10)*—In this condition, the ultrasonic beam must be directed more laterally than in other conditions with dilatation of the right side of the heart.[65,66,97] The echocardiogram is characterized by a large anterior chamber (dependent upon degree of valve displacement) believed to represent the atrialized portion of the right ventricle as well as the ventricle itself, by abnormal motion of the ventricular septum, by decreased rate of posterior motion of the tricuspid valve during diastole (E-F slope) and by more than the usual delay of tricuspid valve closure in comparison to mitral valve closure. A large excursion of the anterior tricuspid leaflet compared with the mitral valve has been reported.

Valvular Pulmonary Stenosis[124-126] — Echoes from the pulmonary cusps are more difficult to record than from the aortic cusps. Echocardiographic features of pulmonary valve motion in this abnormality have only recently been described.[125] Whereas the posterior motion of the pulmonary valve leaflet with atrial systole in normal subjects is slight, it is notably increased in moderate and severe stenosis and does not return to baseline or to a closed position before ventricular systole. This exaggerated leaflet motion is apparently due to increased force of atrial contraction and probably also to a hypertrophied, noncompliant right ventricle.

Valvular pulmonic stenosis may be confused with HISS without outflow obstruction since in severe cases the ventricular septum relative to the LVPW may be asymmetrically hypertrophied.

Aortic Stenosis (Figure 11)†—In adults, a linear relationship exists between the degree of stenosis and the AVO as measured by echocardiography.[130] Also, calcification or abnormal thickness of the valve produces multiple echoes from the cusps during diastole. Reduced AVO has been described but this measurement may not be useful in children because doming of the cusp may be recorded as a normal opening. Moreover, calcification is extremely rare in the pediatric age group. Thus, the value of the echocardiogram in the diagnosis of congenital valvular aortic stenosis is limited. MVVS may be reduced, but this feature is nonspecific. It can be distinguished from the echocardiographic picture of mitral stenosis because of the normal movement of the posterior mitral leaflet and presence of the A point of the mitral valve echotrace. IST and LVPW may be increased but their ratio is similar to that found in normal subjects (in other words, concentric hypertrophy).

In subvalvular aortic stenosis, the following may be seen in an echocardiogram: (1) an abnormal echo in a narrowed outflow tract of the left ventricle during both systole and diastole, (2) rapid and early initial opening of the aortic valve followed by a slower but complete opening with subsequent premature closure so that the cusps are partially closed during the latter part of systole, (3) a fluttering motion of the aortic valves and (4) septal and LVPW thickening with normal ratio, implying concentric hypertrophy.

In supravalvular aortic stenosis of the segmental type (Figure 12), the echoes may reflect a narrowing of the aortic root just above the aortic valve with a normal distal diameter.

Aortic Insufficiency (Figure 13)‡—The major echocardiographic feature is fluttering of the anterior leaflet of the mitral valve due to the regurgitant jet. With severe disease, evidence of premature closure of the mitral valve is seen, and this is generally regarded as a poor prognostic

*References 65,66,97,121,123

†References 46,65,88,93,95,97,101,111,127-136

‡References 95,101,111,117,127,131,137-141

sign.[99,139] Abnormal separation of the aortic cusps during diastole has been described.[95]

Bicuspid Aortic Valve (Figure 14)[142]—Little has been written about the use of echocardiograms in bicuspid aortic valve. Characteristically, there is asymmetric closure of the aortic cusps during diastole because of their difference in size. To determine this, Nanda and co-workers[142] developed the "eccentricity index":

$$\frac{\frac{1}{2} \times \text{ARD at beginning diastole}}{\text{Minimum distance of diastolic cusp echo from nearest aortic margin}}$$

An index of 1.5 or greater was considered indicative of bicuspid aortic valve. In those cases in which the leaflets are equal in width but unequal in length, it may be necessary to angulate the transducer in different positions to record an abnormal index or multiple aortic valve echoes in diastole or both. This has not yet been confirmed by others.

Coarctation of the Aorta[73,99]—An echocardiogram is of no diagnostic value in coarctation of the aorta. However, it is useful in detection of associated lesions such as *bicuspid aortic valve* and *mitral stenosis*. As with acquired mitral stenosis, the congenital variety is characterized by reduced MVVS with loss of the A point of the mitral valve echo (Figure 15). The MVTE and MVDE in this condition may or may not be abnormal. The relation between the degree of mitral obstruction and reduction of MVVS is similar to

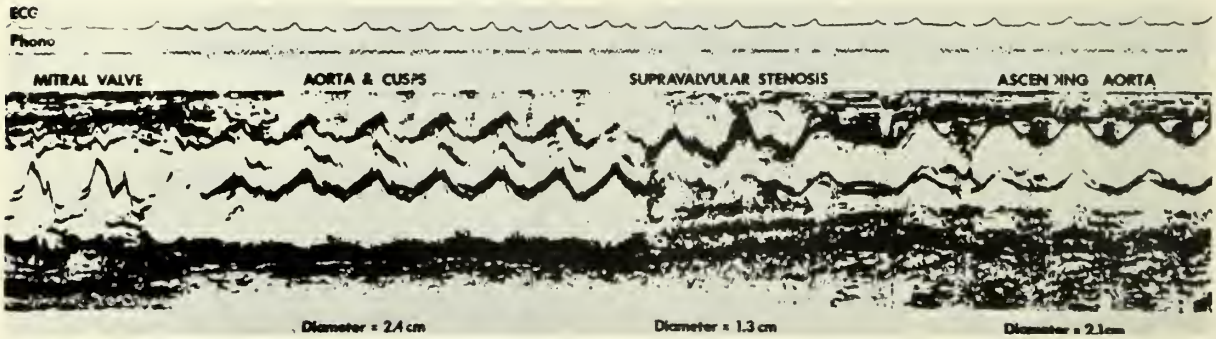


Figure 12.—Continuous strip chart recording of echocardiogram as the transducer sweeps cephalad from the mitral valve showing the narrowing of the aorta from 2.4 to 1.3 cm at the stenotic area and subsequent diameter of 2.1 cm in aorta distal to the stenosis. There are increased echoes at the site of the stenosis. (From Usher BW, et al: Echocardiographic detection of supravalvular aortic stenosis. Circulation 49:1257, 1974, by permission of the American Heart Association, Inc.)

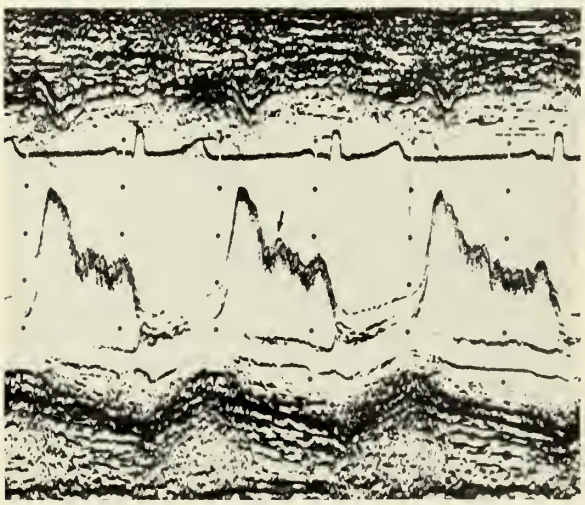


Figure 13.—Echocardiogram of 18-year-old boy with aortic insufficiency. Fluttering of anterior leaflet of mitral valve (arrow) due to regurgitant jet is observed, but in this case there is no evidence of premature closure of mitral valve.

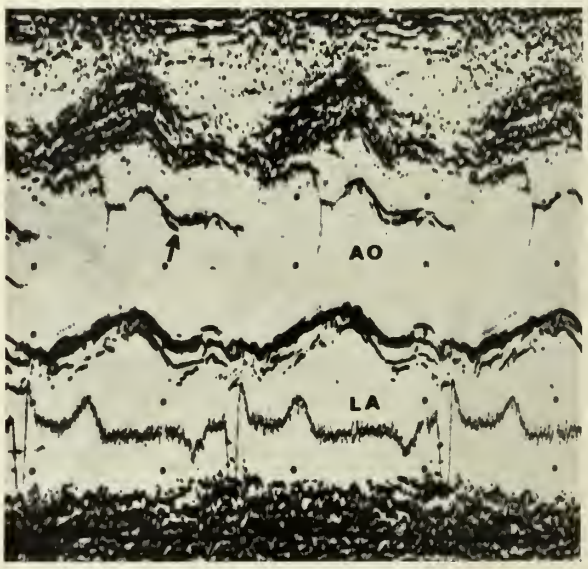


Figure 14.—Echocardiogram in 10-year-old child with bicuspid aortic valve. The displaced aortic valve is identified by arrow. The "eccentricity index" was 2.3. (AO=aorta, LA=left atrium.)

that observed in acquired mitral stenosis. The posterior mitral leaflet usually moves parallel to the anterior leaflet. However, in some patients with mitral stenosis the posterior leaflet motion is normal.[73,143]

Idiopathic Hypertrophic Subaortic Stenosis (IHSS) (Figure 16)*—The echocardiogram is diagnostic. The following features are observed: (1) systolic anterior motion mainly of the anterior mitral leaflet (Figure 16B), which begins shortly after the onset of systole due to malalignment of the anterior papillary muscle and malposition of the mitral valve, (2) approximation of the anterior mitral leaflet to the ventricular septum sometimes with an unrecognizable E point (Figure 16A), (3) narrowing of the left ventricular outflow tract in late systole positively correlated with duration and amplitude of the anterior systolic movement of the mitral valve (obstructive index),[150] (4) reduced MVVS, (5) thickening of the ventricular septum (Figure 16A) with a thickness which exceeds that of the LVPW (a ratio, except in infants,[152] greater than 1.3:1), (6) decreased amplitude of contraction of ventricular septum with little change in thickness during systole compared to diastole, (7) abnormal partial midsystolic closure of aortic cusps followed by late systolic reopening, (8) reduced LVD (inconstant), (9) anterior location of mitral valve and (10) provocation or exaggeration of abnormal mitral valve movement following premature ventricular contraction, administration of isoproterenol, administration of amyl nitrite, the valsalva maneuver or following exercise.

*References 48-50,54,60,65,88,99,111,117,128,140,141,144-152

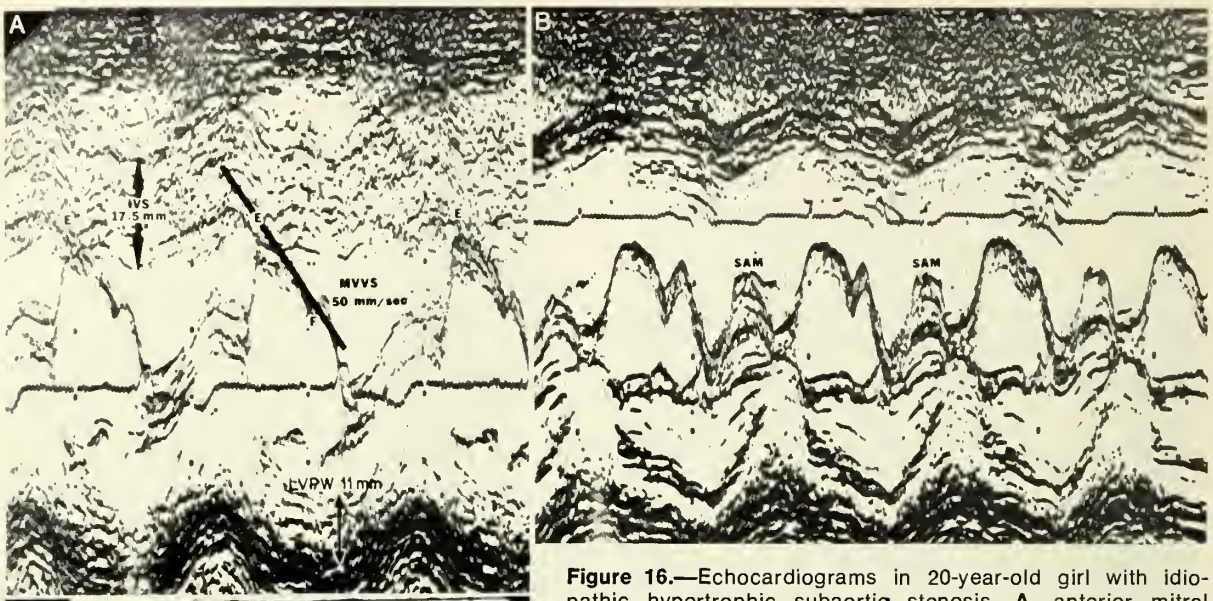
Figure 15.—Echocardiogram of 14-year-old girl with congenital mitral stenosis. Configuration of anterior leaflet (AMV) is abnormal with loss of A point and decreased mitral valve velocity slope (MVVS).

Asymmetrical septal hypertrophy has been observed in lesions other than IHSS.[152,153] In some patients with right ventricular pressure overload with pulmonic stenosis or pulmonary hypertension, there will be echocardiographic findings of asymmetrical septal hypertrophy as a reflection of right ventricular hypertrophy. In infants this septal thickening disproportional to left ventricular posterior wall thickness may be seen in absence of cardiac disease but as a reflection of right ventricular preponderance of the newborn.[152] There are also patients with nonobstructive cardiomyopathy with asymmetrical hypertrophy.[153]

Anomalous Origin of Left Coronary Artery[154]—Only one report (abstract) could be found in the literature. Echocardiograms were described in four patients. The features were: (1) dominance of right coronary cusp in all, (2) posterior dislocation of aortic valve in all, (3) posterior position of mitral valve and increased LVD with poor LVPW motion in two, (4) aneurysmal dilation of lower part of the left ventricle in two and (5) abnormal septal motion in one.

Cor Triatriatum[55,73,118,155]—Little information is available regarding the echocardiogram. Lundstrom[55] demonstrated an abnormal echo posterior to the anterior mitral leaflet which was separated from the echo of the LVPW. This abnormal echo had greater movement with atrial systole than with ventricular systole. Lundstrom assumed that the abnormal echo originated from a membrane dividing the left atrium into two compartments.[55] Paquet[118] showed an echo-free space *behind* the left atrium and not extending to the left ventricle. He assumed that this represented the third chamber in his patient with cor triatriatum.

Primary Pulmonary Hypertension[107,125,156,157]—The following features have been described: (1) reduced MVVS similar to that seen in mitral stenosis but with no abnormal motion of the posterior leaflet, (2) increased RVD, (3) septal thickening with a IST/LVPW ratio greater than normal, (4) systolic mitral valve prolapse, (5)



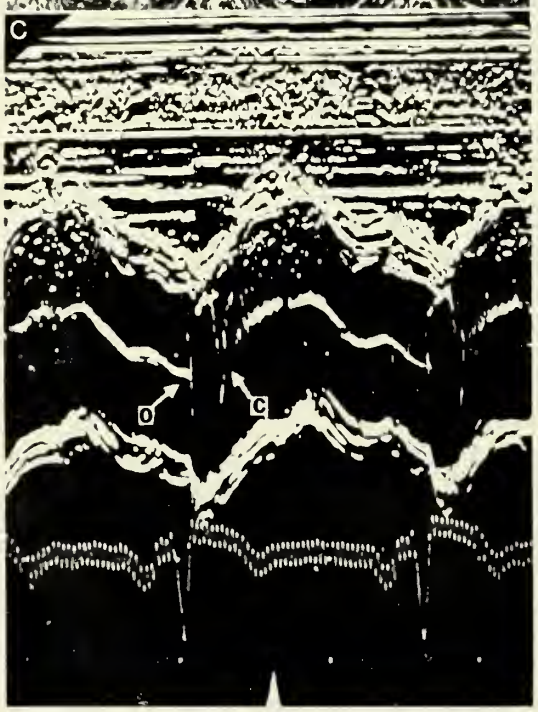


Figure 16.—Echocardiograms in 20-year-old girl with idiopathic hypertrophic subaortic stenosis. **A,** anterior mitral leaflet reaches the interventricular septum (IVS) during early diastole, and E point is not distinguishable. Mitral valve velocity slope (MVVS) is reduced. Ventricular septum is thickened and is greater than left ventricular posterior wall (LVPW), the ratio being 1.7:1. **B.** anterior motion of mitral valve during late systole (SAM) is considered one of the characteristics of this condition and causes narrowing of outflow tract of left ventricle. Asymmetric septal hypertrophy is not visualized in this position. **C,** opening of the valve (O) is early in systole and closure (C) occurs in mid-systole.

abnormal septal motion consistent with pulmonic insufficiency or tricuspid insufficiency, (6) minimal or absent pulmonic cusp motion in mid and late diastole and (7) delayed but abrupt opening movement of the pulmonic valve.

Gramiak and co-workers[124] and Weyman and associates[125] recently described no posterior movement of the pulmonary valve with atrial contraction as a characteristic of pulmonary hypertension.

d-Transposition of Great Arteries (Figure 17)*—The echocardiogram shows both semilunar valves recorded simultaneously and the great vessels are superimposed without an intervening crista. The vessel in continuity with the mitral valve is the pulmonic valve. It can be identified by the following echocardiographic features: (1) the interval between the R wave of the electrocardiogram and the onset of closure of the semilunar valve is larger for the pulmonary artery in the absence of pulmonary hypertension[159,162] and (2) in the absence of pulmonic stenosis, the root diameter is larger in the pulmonary artery than in the aorta.

Corrected Transposition†—This is difficult to distinguish by echocardiogram from single ventricle because the ventricular chambers lie side by side, and the ventricular septum is perpendicular to the anterior chest wall. Thus, it is parallel to the ultrasonic beam and usually its echoes cannot be recorded. The mitral valve is to the right, and the tricuspid valve is to the left. Differentiation of the two valves can be made on the basis of atrioventricular (mitral) valve to semilunar valve continuity. The location of the mitral valve identifies

*References 59,61,62,71,73,88,99,100,124,158-163

†References 61,65,73,88,97,159,162,163

the left ventricle. Registration of parallel echoes from two of three leaflets of the tricuspid valve has been reported.[65]

The spatial relationship of the great vessels is important in differentiating this condition from complete d-transposition of the great arteries. The echoes from the anterior vessel lie to the left and represent the aorta. The interval between the R wave of the electrocardiogram and closure of the cusps is shorter than in the pulmonary artery which is to the right and posterior.

Tetralogy of Fallot (Figure 18)*—The most important echocardiographic feature is evidence of discontinuity of the ventricular septum and the anterior wall of the aorta (that is, overriding aorta). As the ultrasonic beam sweeps from the cardiac apex superiorly, echoes from the ventricular septum disappear abruptly over the septal defect and then reappear at the overriding aorta. Although aortic-mitral discontinuity has been described,[164] continuity of these structures is characteristically preserved and helps to distinguish tetralogy from double outlet right ventricle in the absence of left ventricular enlargement.

ARD and RVD are usually increased, and the ratio of right ventricular outflow tract to left atrium suggests narrowing of the outflow tract. In most cases, fluttering of the mitral valve during diastole is observed. This is due to turbulence arising from the right-to-left ventricular shunt rather than from the aortic valve.[166]

Registration of echoes from the pulmonic valve and evidence of an outflow tract anterior to the aorta exclude truncus arteriosus.

Tricuspid Atresia (Figure 19)†—The echocardiogram may be indistinguishable from that of single ventricle since sometimes the ventricular septum cannot be identified, and a single atrioventricular valve with exaggerated anterior motion may be present. A tricuspid valve echo cannot be recorded. In some cases, the right ventricle can be identified as a minute anterior chamber and this then establishes the diagnosis of tri-

*References 46,62-64,71,95,99,100,164,165

†References 51,59,65,71,88,90,97,99,100,107

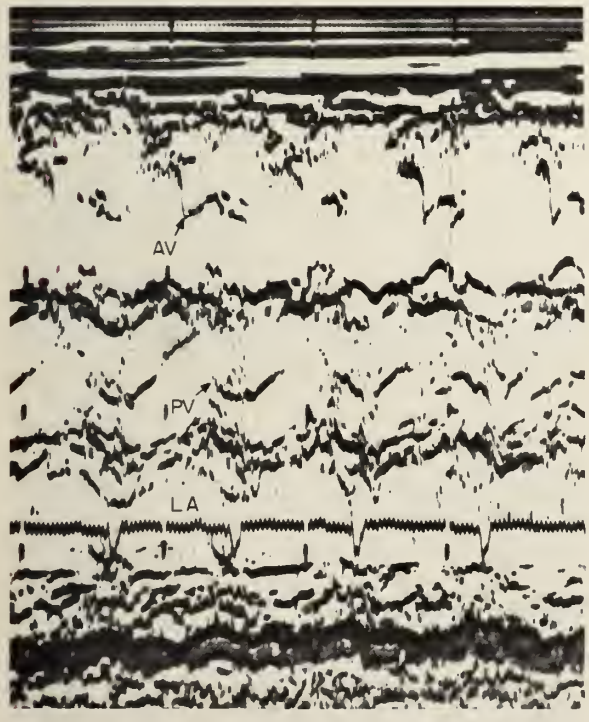


Figure 17.—Echocardiogram of 2-day-old infant with d-transposition of great vessels. The transducer was positioned at the third left parasternal space and directed slightly superiorly and medially from mitral valve. Both semilunar valves are recorded simultaneously, and pulmonary valve (PV) closure is delayed in comparison to aortic valve (AV) closure. (LA=left atrium.)

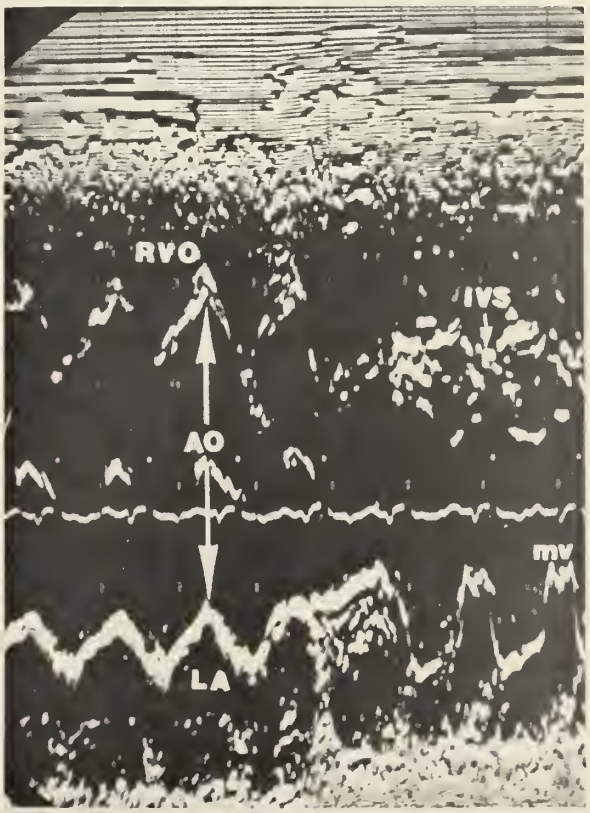


Figure 18.—Echocardiogram in 11-year-old child with tetralogy of Fallot. Note large aorta (AO) overriding ventricular septum. Left atrium (LA) is small in comparison with aorta. (mv=mitral valve, IVS=interventricular septum, RVO=right ventricular outflow.)

cuspid atresia. LVD as well as MVTE are at or above the upper limit of normal. Aortic-mitral valve continuity is preserved.

Pulmonary Atresia[71,90,167]—The echocardiographic features are similar to those seen in tricuspid atresia. LVD as well as MVTE are at or above the upper limit of normal. When the right ventricle is recorded, RVD is usually reduced. Echoes from the pulmonary valve cannot be recorded. If echoes can be recorded from the tricuspid valve, tricuspid atresia is excluded.

Hypoplastic Left Ventricle (Figure 20)*—In selected cases where the echocardiographic findings are consistent with the clinical impression, cardiac catheterization studies are considered by some to be unnecessary.[59,97,99] The characteristic features are: (1) increased RVD with exaggerated excursion of the tricuspid valve, (2) existence of a very small left ventricular cavity posteriorly when demonstrable, (3) ARD is reduced to at least half normal, and aortic valve echoes are not seen.

*References 51,55,59,65,71,73,88,97,99,115,168,169

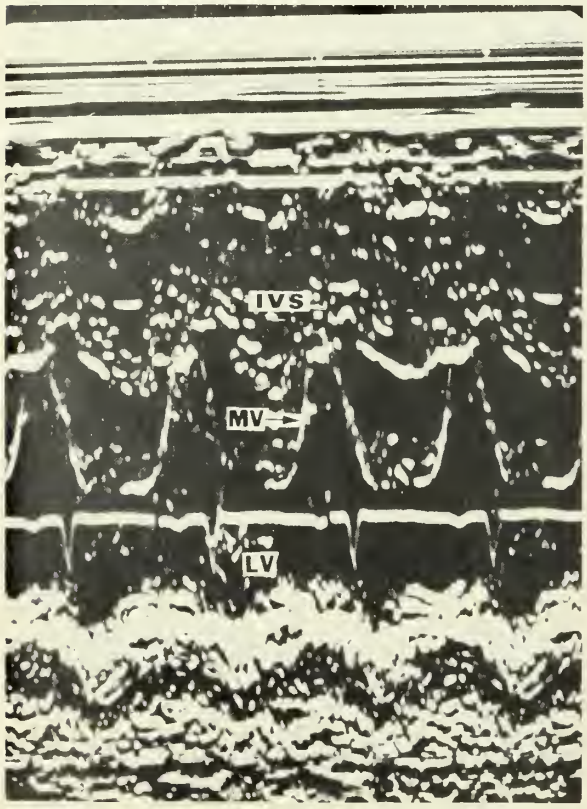


Figure 19.—Echocardiogram of 3-day-old neonate with tricuspid atresia. Right ventricular chamber is small, and a single atrioventricular valve with exaggerated anterior motion is present. (IVS=interventricular septum, MV=mitral valve, LV=left ventricle.)

With hypoplasia of the mitral valve, only the A point is recorded, since the valve opens only during atrial systole. With complete atresia of the mitral valve, echoes from the mitral ring may be recorded (anterior movement with systole, and posterior movement with diastole).

Single Ventricle (Figure 21)†—The most important feature is inability to demonstrate the ventricular septum. If two separate atrioventricular valves are present, their echoes are recorded at different levels; if only a single valve is present, its anterior excursion is accentuated, and it may approach the anterior ventricular wall. This abnormal anterior movement should suggest the possibility of a single ventricle, and a careful search for the ventricular septum must be made.

Double Outlet Right Ventricle (Figure 22)‡—The cardinal echocardiographic feature had been thought to be discontinuity of the mitral valve and aortic root. Both great arteries anterior to the ventricular septum may also be demonstrated. The most posterior portion of the anterior mitral valve leaflet lies as much as 1.8 cm below the posterior wall of the aorta.[88]

Double outlet right ventricle must be distinguished from other lesions which cause aortic-mitral valve discontinuity including endocardial cushion defect,[90] single ventricle[99] endocardial fibroelastosis[170] and other lesions with left ventricular dilatation.[171]

Persistent Truncus Arteriosus§—The echocardiogram may be confused with that of tetralogy of Fallot, since in both conditions there is a large overriding vessel with interruption of the ventricular septum. However, in truncus arteriosus, there is no echo-free space anterior to the root vessel, and LAD is increased.

Cardiac Malposition[89,162,163,172] — Analysis of the echocardiogram is largely deductive. One must first ascertain the atrial situs by radiography. If the apex is on the left, the transducer is positioned in the conventional location; if it is on the right, the transducer is placed in a corresponding position to the right sternal border. Echocardiographic interpretation assumes significance only when the location of the transducer and the angulation of the beam are known. The mitral and tricuspid valves can be identified by their continuity or discontinuity with the semilunar valves. The pulmonary and aortic valves are identified as

†References 51,55,71,73,88,90,99
‡References 53,73,88,92,97,99,100,170,171
§References 64,71,73,97,98,100

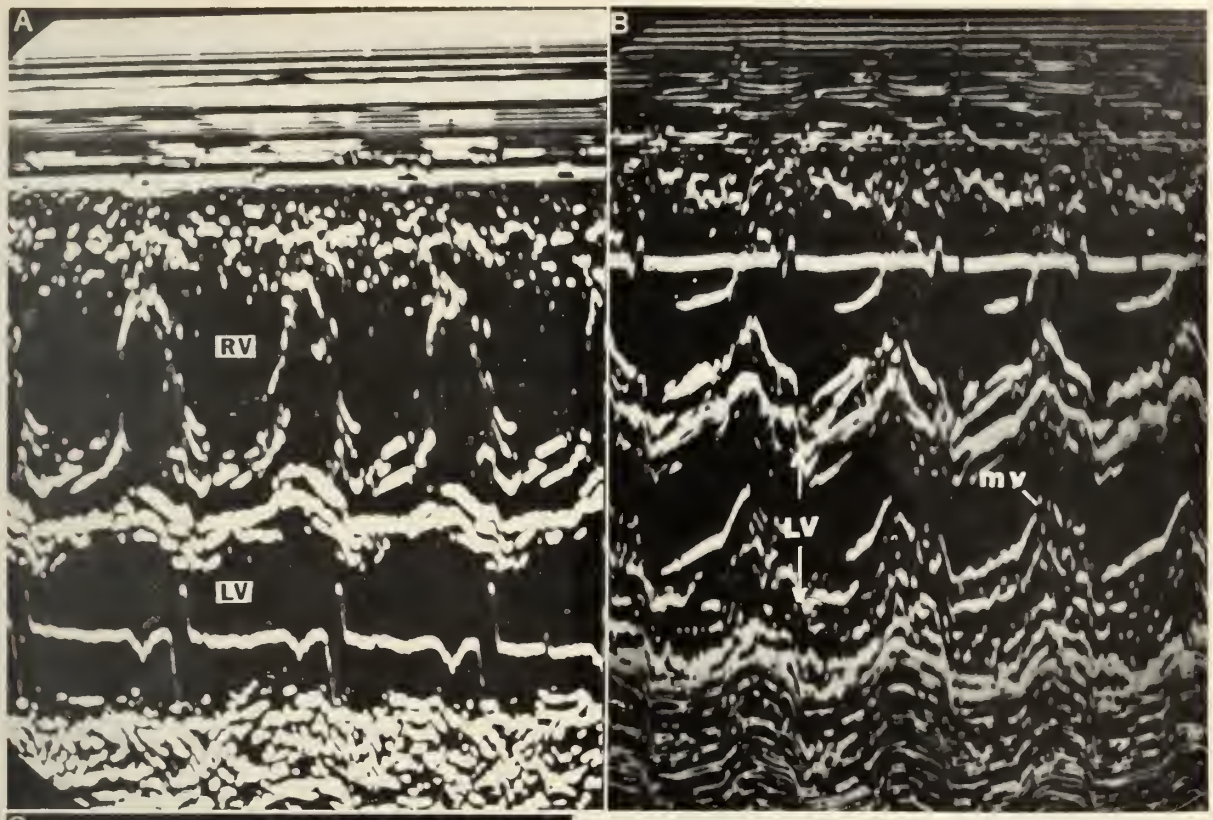


Figure 20.—Echocardiograms in 2-day-old infant with hypoplastic left ventricle. **A,** exaggerated excursion of tricuspid valve is illustrated. **B,** tracing shows small left ventricular cavity, measuring 7 mm (normal for patient's size = 16-21 mm). A mitral valve was present in this case but abnormal. **C,** both aortic diameter and left atrial dimension are small compared to right ventricular outflow tract. (RV = right ventricle, LV = left ventricle, mv = mitral valve, RVO = right ventricular outflow, AO = aorta.)

described under *Transposition of the Great Arteries*. Because of the frequency of single ventricle and of complete atrioventricular canal, a careful search must be made for the ventricular septum. With the above data, the ventricular loop and the relation of the great arteries to the ventricles can be assessed.

Comment

Echocardiography is an established procedure of proven value in acquired heart disease. It has recently become an established procedure also in the broad area of congenital heart disease but has not been evaluated in sufficiently large numbers for many of the individual lesions. Moreover, the features described for some of the defects may not be demonstrable in the neonatal period since the magnitude of the pathophysiology may not be

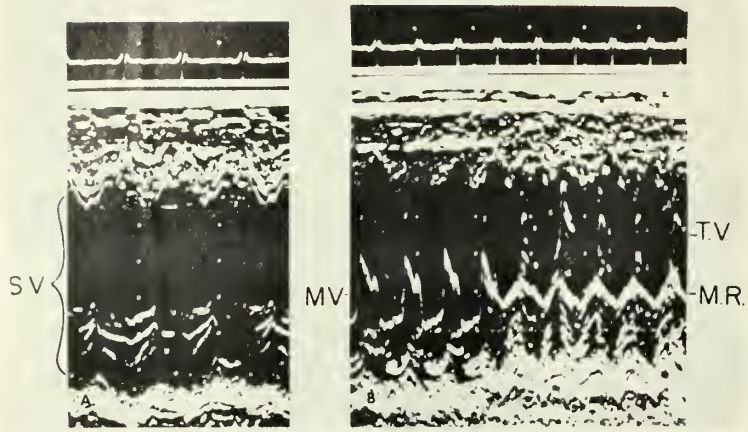


Figure 21.—Echocardiogram of patient with single ventricle and transposition of great arteries. **A**, septum was not identified; **B**, shows two atrioventricular valves. (SV=single ventricle, MV=mitral valve, TV=tricuspid valve, MR=mitral ring.) (From Meyer RA, Kaplan S: Noninvasive techniques in pediatric cardiovascular disease. Progr Card Dis 15:341, 1973.)

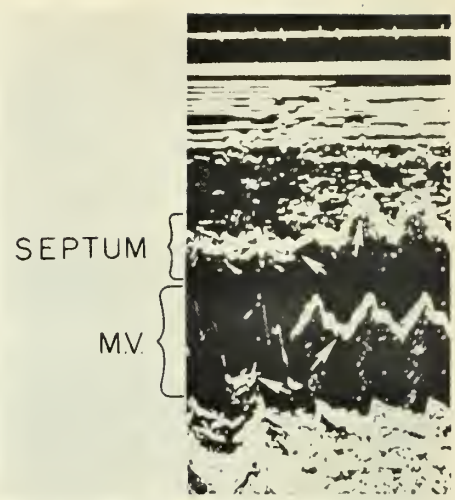


Figure 22.—This echogram of double outlet right ventricle shows discontinuity of mitral valve and aortic root. There is abrupt anterior displacement of aortic root from systolic position of mitral valve (lower arrows). Anterior displacement of the aorta is shown by the upper arrows. The septal and anterior aortic root echoes should be at the same depth. (MV=mitral valve.) (From Meyer RA, Kaplan S: Noninvasive techniques in pediatric cardiovascular disease. Progr Card Dis 15:341, 1973.)

expressed for some time. Finally, because of the wide age range that congenital heart disease encompasses, many more measurements in normal infants and children of all ages are needed before the limits of normal can be precisely defined.

The echocardiogram is currently viewed as a valuable adjunct for diagnosis in congenital heart disease. Its potential in this area seems almost unlimited, and there is good reason for the general enthusiasm which its advent has generated. Development of segment and multiple crystal scanning promises to make it even more valuable than originally envisioned. It is because of this tremendous potential and the accompanying universal enthusiasm that mention of certain caveats would seem to be in order:

- Normal limits of the various measurement parameters have not yet been clearly defined for the pediatric age group.
- Failure to demonstrate a given structure does not *necessarily* mean it is not present.
- The position of the transducer on the chest wall may either mask or artificially produce important features; for example, overriding aorta or discontinuity of the mitral valve and posterior aortic wall.
- The value of echocardiograms for assessment of ventricular volumes and function has not been firmly established in infants and children.
- The tentative clinical diagnosis must be known to the operator.
- The operator must be familiar with the anatomic characteristics of the various congenital heart lesions.
- The position and angulation of the transducer must be known to the interpreter.
- Ideally, the operator and interpreter should be one and the same—a physician well versed in congenital heart disease as well as in echocardiography.

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Refer to: Toxic megacolon—Medical Staff Conference, University of California, San Francisco. West J Med 124:122-127, Feb 1976

Toxic Megacolon

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. RECTOR:* *Grand Rounds this morning will begin with a discussion of toxic megacolon. Dr. Mark Rosenberg, chief fellow in Gastroenterology at the Moffitt Hospital, will lead the discussion and will begin by giving the presentation of a very interesting case history.*

Case Summary

DR. ROSENBERG:† The patient for discussion today, a 62-year-old white man, was in his usual state of health until late April 1975 when the sudden onset of crampy, lower abdominal pain developed followed by a profuse, watery, nonbloody diarrhea not associated with fever, chills or tenesmus. He had not been traveling and none of his acquaintances were similarly afflicted. The patient was seen by his personal physician who noted hyperemia and friability on sigmoidoscopy. Routine cultures of stool specimens from this sigmoidoscopy were negative as were tests for ova and parasites. He was given diphenoxylate hydrochloride with atropine sulfate (Lomotil®) for the diarrhea and a liquid diet was recommended. However, during the next week to ten days, profuse watery diarrhea continued—up to 30 bowel movements per day—and on May 23, 1975 the patient was admitted to another hospital because of continued diarrhea, dehydration and weakness.

The medical history was pertinent in that hypertension was present, treated only sporadically in the past. Also, the patient had recently taken ibuprofen (Motrin®) for bursitis of the shoulder. Surgical history included an open reduction of a right hip fracture in 1971. The patient was a sporadic drinker who was given to binges and there existed a question of amphetamine abuse in the recent past. The family history was noncontributory. There was no history of inflammatory bowel disease.

On physical examination the patient was unhealthy appearing, very uncooperative and rather childish in his actions. Blood pressure was 96/60 mm of mercury, pulse rate 100 beats per minute, temperature 98°F (36.7°C) and respirations 20. Findings on examination of the head, eyes, ears, nose and throat were unremarkable. The chest was clear and other than a grade I/VI systolic ejection murmur, results of cardiovascular exami-

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Figure 1.—X-ray film of the abdomen showing significant dilatation of the transverse colon.

nation showed no abnormalities. The abdomen was soft, nontender and nondistended. Bowel sounds were present. There were no masses or organomegaly. A right inguinal hernia was present. Results of neurological studies were within normal limits. A stool guaiac test gave negative findings.

Laboratory studies disclosed the following values: leukocyte count, 12,800 per cu mm with a left shift; hematocrit reading, 38.1 percent; platelets, 800,000 per cu mm. There was hyponatremia and hyperkalemia, and dehydration was evidenced by a blood urea nitrogen (BUN) value of 43 mg per 100 ml. Other pertinent laboratory data included a low albumin of 2.9 grams per 100 ml. Gram stain of stool showed many polymorphonuclear cells. On x-ray films of the abdomen, a transverse colon diameter of 6 cm was noted.

The patient was first treated with intravenous hydration and nasogastric suction. However, soon after admission he became febrile and the leukocytosis with left shift became more pronounced. Results of cultures done before the institution of antibiotic therapy were negative. His mental status changed notably. He became confused, disoriented and obstreperous. On x-ray studies of the abdomen, progressive dilatation of the transverse colon to approximately 8 to 9 cm in diameter was noted. Sigmoidoscopy was repeated and classic findings of ulcerative colitis (granularity, friability and ulceration) were observed. The clinical features of the case were felt to be most consistent with the toxic megacolon of ulcerative colitis and the patient was transferred to the University of California Medical Center following minimal response to treatment for 24 hours with hydrocortisone (Solu-Cortef®), penicillin and gentamicin.

On admission to Moffitt Hospital, the patient was found to be confused and abusive. Blood pressure was 100/60 mm of mercury, pulse rate 90 beats per minute and temperature 99.3°F (37.4°C). Findings on physical examination were similar to those previously noted except that the abdomen was found to be distended and a large loop of bowel could be palpated in the upper part of the abdomen. Bowel sounds were diminished but the abdomen remained nontender. Laboratory data on admission included a normal leukocyte count and differential, hematocrit reading of 31 percent and platelet count of 549,000 per cu mm. Values for electrolytes, BUN and creatinine had improved from the first admission. The patient remained hypoalbuminemic and on an x-ray film of the abdomen, dilatation of the transverse colon to 9 cm in diameter (normal less than 6 cm) was seen (Figure 1). One stool culture taken on the original admission returned positive for Shigella group B.

The patient's hospital course over the next three days was one of a slow downhill progression. A regimen for toxic megacolon was continued with ampicillin being substituted for the penicillin. However, leukocytosis with a left shift again developed and toxic granulations were seen on the peripheral blood smear. The albumin value dropped to 1.8 grams per 100 ml. Though the patient was at first afebrile, the temperature spiked to 38.5 on May 30. On x-ray films of the abdomen, progressive colonic dilatation continued to be seen. Findings on sigmoidoscopy included the granularity, friability and ulcers noted before, plus the new appearance of numerous pseudopolyps. Workup of metabolic encephalopathy and of a right pleural effusion observed on x-ray studies were unrevealing. On May 30, five days after clinical features of toxic megacolon developed, subtotal colectomy, with ileostomy and sigmoid mucous fistula, was carried out.

TABLE 1.—*Criteria for Diagnosis of Toxic Megacolon**

1. Evidence of dilatation
   Clinical: Visible abdominal distention and/or peritonism (rebound tenderness)
   Radiological: Segmental or total colonic distention with or without pseudopolypi
2. Evidence of toxicity
   a. Pyrexia >101.5°F
      Tachycardia >120 per min
      Leukocytosis >10,500 per cu mm
      Anemia-hemoglobin <60 percent
   b. Dehydration
      Mental changes
      Electrolyte disturbance
      Hypotension
3. Subsequent pathological confirmation of dilatation and transmural extension of the inflammatory process

*Should include three of four from 2a and one of four from 2b.

TABLE 2.—*Diseases Associated with Toxic Megacolon*

Ulcerative colitis	Typhoid fever
Granulomatous colitis	Cholera
Amebiasis	Bacillary dysentery

Discussion

During the next few minutes I am going to discuss the entity of toxic megacolon. We will, however, keep returning to this patient whose case I believe represents a very fascinating and unusual variant of this dreaded complication of inflammatory disorders of the bowel.

There are a host of disease entities that can present as a megacolon. These range from congenital megacolons, of which Hirschsprung's disease is the best known, to the acquired forms of megacolon, including psychogenic, metabolic and neurologic forms, and those associated with generalized muscle diseases. While findings on x-ray studies may be similar, the clinical courses are so different they should never be confused. I have elected to spend the time this morning discussing the toxic form of megacolon.

I want to stress at the outset, that this is a diagnosis that can only be made on clinical grounds. There is no blood test that is definitive, no x-ray study that by itself is pathognomonic, no sigmoidoscopy that alone clinches the diagnosis. Toxicity is difficult to define and, although attempts have been made to establish objective criteria, there are often borderline cases in which it becomes necessary to entirely rely upon clinical judgment. The patient will usually have a past history of inflammatory bowel disease and will present with diarrhea which is often bloody, abdominal pain, evidence of abdominal distention and evidence of toxicity, manifest by fever, tachycardia and leukocytosis. Jalan[1] has established criteria for this diagnosis (Table 1). Our patient today, I feel, meets their clinical criteria.

Toxic megacolon has been implicated in a number of different disease states (Table 2). In the United States, the differential diagnosis really revolves around ulcerative colitis, granulomatous colitis, amebiasis and possibly bacillary dysentery.[2] Typhoid fever is rare and cholera is nonexistent here. Curiously, there are no documented case reports of toxic megacolon in bacillary dysentery, although most authors include it in their differential diagnosis.[3] Our patient today may represent such a case. There are, however, a few case reports of toxic megacolon in patients with amebiasis.[4] To gastroenterologists and internists, this is a most frightening consideration, since our therapy generally includes large doses of steroids. In the last few years we have seen two or three patients die of disseminated amebiasis while being treated for what was thought to be idiopathic ulcerative colitis. Amoeba, therefore, must be conclusively ruled out or covered for until findings from appropriate cultures and serologic studies are considered.

Granulomatous colitis has also been implicated as a cause of toxic megacolon, although at a much lower rate than seen in idiopathic ulcerative colitis.[5] It has been reasoned that toxic dilatation would be unlikely because the transmural proliferation and fibrosis that occur in granulomatous colitis would prevent the colon from dilating. This complication, therefore, would likely occur early in the course of the disease before extensive fibrosis has taken place.[6]

Most cases of toxic megacolon will be seen in association with ulcerative colitis. It was first recognized as a distinct clinical entity in the early 1950's, although there are case reports mentioned as far back as the thirties. It is an uncommon but by no means rare complication of ulcerative colitis. The literature quotes an occurrence rate of approximately 2 to 5 percent in most large, unselected series of idiopathic ulcerative colitis.[7,8] However, it is likely that if more severe cases of ulcerative colitis were selected, the percentage would climb much higher. There is a fairly even distribution in all age groups. Most authors report an even sex ratio.

In most patients pancolitis is present and there seems to be no relationship to the duration of the disease. Interestingly, 25 to 40 percent of cases

TABLE 3.—*Predisposing Factors in Toxic Megacolon*

Anticholinergics	Aerophagia
Narcotics	Pregnancy
Barium enema	Lomotil
Hypokalemia	

of toxic megacolon are seen during a patient's first attack of ulcerative colitis. In Drs. Sleisenger's[9] and Kirsner's[2] series, a fourth of the patients presented during their first attack of ulcerative colitis. In Jalan's series,[1] is was closer to 40 percent. Of interest is the fact that most cases developed while the patients were in hospital.

What sets off the chain of events that leads to the clinical features of toxic megacolon remains a mystery. However, a number of possibly precipitating factors have been implicated (Table 3).

Dr. Sleisenger[9] and his group at Cornell were among the first to implicate the role of anticholinergics and narcotics on colonic dilatation. Anticholinergic drugs, in their usual therapeutic doses, can exert an inhibitory influence on colonic motility. Narcotics are powerful inhibitors of propulsive activity of the colon. Manometric studies of the pelvic colon and rectum in active ulcerative colitis have shown decreased to absent "phasic activity" and an abnormal incidence of nonperistaltic mass movements.[10] It seems logical to conclude that the abnormal motility pattern seen in active ulcerative colitis, plus the altered motility produced by anticholinergics or narcotics, could lead to the atonic, nonpropulsive colon characteristic of toxic megacolon. The inability of the distended colon to empty contributes to further dilatation by fluid and gas, and also results in an overflow diarrhea. In Kirsner's series,[2] 50 percent of patients had been taking narcotics and greater than 90 percent had received anticholinergics. In Sleisenger's series, 75 percent had had this combination.[9]

The barium enema has also been implicated as an inciting event in most series on toxic megacolon.[1-3,11] In a third to a half of the cases, it has been ordered usually within the preceding two weeks. The potential role of the barium enema in precipitating toxic megacolon is reflected by the fact that the intraluminal pressure during the examination is in the range of 90 ml of water pressure, thus exceeding pressures usually measured in normal colons during peristalsis. This could further diminish blood flow in an already severely diseased colon. A minority of observers, including Henry Goldberg in the University of California, San Francisco, Department of Radiology,[12] question the etiological role of the barium enema precipitating toxic megacolon. But even Dr. Goldberg would agree, I think, that there is no place for this procedure during an episode of toxic megacolon.

TABLE 4.—*Radiologic Criteria for the Diagnosis of Toxic Megacolon*

1. There is a pronounced distention of one or several parts of the colon. The usual diameter of the colon is less than 6 cm. In the average case of toxic megacolon, the diameter is approximately 9 to 10 cm and ranges from 6 to 15 cm.
2. Obliteration of the haustral and mucosal pattern.
3. Irregular contours of the colon with multiple deep projections indicative of ulceration.
4. Numerous nodular, pseudopolypoid intraluminal lesions.
5. A lack of redundancy or a relative shortening of the colon.
6. Inability of the colon to contract normally due to loss of tone. The transverse colon is most often involved. This is probably due to the fact that with the patient standing or supine, air rises to the highest segment. The descending colon and sigmoid are the next most frequently involved. (Adapted from Wolf and Marshak.[19])

Hypokalemia has been implicated in approximately half of the cases, but vigorous therapy to correct the calculated total body deficit has not in any instance changed the clinical course.

Pregnancy has been implicated in a few cases reported in the literature.[13]

The Lomotil story is interesting and may have a bearing upon our patient this morning. Lomotil therapy increases tone and decreases propulsive activity of the colon. DuPont,[14] in an article on the adverse effects of Lomotil therapy in shigellosis, mentions that he and his associates have seen two patients with schigellosis in whom features of toxic megacolon developed after Lomotil therapy was begun. They point out that diarrhea in bacterial infection is protective because it decreases the contact time between the organism and the mucosa and thereby decreases the chance for invasion. They therefore question the safety of this drug used in this circumstance. Pittman[15] also mentions a group of patients with inflammatory bowel disease in whom toxic megacolon developed during treatment with Lomotil. These patients were unusual in that surgical therapy was not needed and a much milder mucosal disease was present than is usually seen in toxic megacolon.

Next I would like to turn to the features seen

TABLE 5.—*Management of Toxic Megacolon*

1. Bowel decompression—usually a nasogastric tube will suffice.
2. Fluid and electrolyte replacement. These patients are profoundly hypoalbuminemic and albumin in some way must be replaced.
3. Blood transfusions.
4. Antibiotic coverage—since impending perforation is always a threat, it is imperative to cover for anaerobes.
5. Steroid therapy—the tendency in medicine is to use steroids in just about all desperate situations. In toxic megacolon, they do two things. They keep the steroid-dependent patient from going into adrenal crisis under the added stress of the toxicity. Also with steroid therapy the fever will usually diminish and the leukocyte count will come back toward normal. There is also no evidence that they increase the percentage of perforations. However, whether they change the ultimate course of toxic megacolon is subject to conjecture. My prejudice is that they do not.

TABLE 6.—*Indications for Surgical Operation*

1. Impending perforation
2. Perforation
3. Severe hemorrhage
4. Deteriorating clinical course after 24 to 72 hours of maximal medical therapy

on x-ray studies in this disease entity. Although barium enema is contraindicated, the diagnosis can be confirmed on plain film. In terms of the radiologic differential diagnosis, other entities which produce megacolon do not show evidence of severe, intrinsic inflammatory disease of the bowel wall. The radiologic criteria for diagnosis of this entity are outlined in Table 4.

The pathological findings in toxic megacolon are well differentiated from those in ulcerative colitis. The inflammatory process is transmural with pronounced muscle destruction and serosal involvement. In most cases there is complete loss of the muscularis with destruction of both the longitudinal and circular muscle layers. In ulcerative colitis, the inflammatory response rarely goes past the submucosa. Whether or not Auerbach's plexus, which reside between the two muscle layers, are destroyed or damaged remains controversial. All authors agree that it is the loss of muscle tone and coordination that leads to the dilatation. One author[16] described the situation as a third degree burn, bathed in feces, and with this vivid picture in mind it is not hard to understand the resultant anemia, hypoalbuminemia and electrolyte disorders so commonly seen. The management of toxic megacolon is critical and has been outlined in Table 5.

In the patient presented today, maximal therapy failed and a subtotal colectomy was carried out. Unfortunately, this case history is the rule rather than the exception in toxic megacolon. In most series, between 75 and 90 percent of patients will require surgical operation.[11] The indications for operation appear in Table 6. It is important to note that it is usually impossible to predict impending perforation in a patient taking large doses of steroids because fever, leukocyte count and tachycardia usually return toward normal. Even with perforation, an abdominal examination may disclose no abnormalities. The mortality following perforation is 60 percent.[9] However, most patients are sent to surgery because of a failure of maximal medical therapy. Binder has reviewed all the series on toxic megacolon in the literature up to 1971.[11] He found that the percentage of patients successfully managed by medical means alone was less than 30 percent. In these medically treated patients, the mortality rate was 25 percent, with most of the deaths occurring in the patients in whom perforation was present. The overall surgical mortality is also very high—22 percent. However, most of the mortality is from operating on patients in whom perforation occurred while under the watchful eye of the internist. Surgical mortality in those cases where perforation was not present is less than 10 percent. Recently there have been two large series published. Both groups of workers followed the tenets of management outlined here, and there was a combined mortality of less than 5 percent.[6,11] I find this a very encouraging set of statistics.

In the remaining few minutes, I would like to return to the patient presented this morning. We waited longer than the usual 24 to 72 hours because a culture for Shigella was positive, and because of our reluctance to operate in the presence of a possibly invasive shigellosis presenting as a toxic megacolon. However, when the patient's condition did not respond to maximal medical therapy—which included appropriate antibiotic therapy—and continued to deteriorate clinically—as manifested by anemia, profound hypoalbuminemia, mental deterioration combined with the new finding of pseudopolyps on sigmoidoscopy, and continued colonic dilatation—our hand was forced. At operation, the colon was found to be dilated but not particularly thinned. Furthermore, the microscopic features of the colon were not those usually associated with toxic megacolon.

The patient's postoperative course was uneventful, with return of mentation to normal within a week. Of further interest is the fact that on sigmoidoscopy, three months following colectomy, the remaining 20 cm of rectum was found to be completely normal. That this should occur in the setting of idiopathic ulcerative colitis is exceedingly rare, thus suggesting another diagnosis.[17,18]

In summary, I can only speculate that in our patient idiopathic ulcerative colitis was not present and that the positive culture for Shigella was accurate. Therapy with Lomotil, by increasing intestinal transit time, allowed for prolonged contact between the organism and the colonic epithelium, thereby enhancing its invasiveness. It may also have contributed to mechanical circumstances favoring colonic dilatation. Administration of antibiotics may have eradicated the bacterial infection, but by that time an irreversible chain of events had been started which led to the development of toxic megacolon.

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Premenstrual Tension Resembling Relapse into Depression or Psychosis

When my nurse gets a phone call from a patient who seems to be slipping back (into a depressed or psychotic state), and if it's a woman, I have her immediately inquire if the woman is menstruating or about to menstruate because quite often, in that premenstrual situation, they do have some symptoms which could resemble the beginning of a relapse and yet they are not. An astute clinician can make that distinction simply by discussing it with the patient on the telephone and not immediately putting the patient back on medication. This is a very important point that many doctors overlook.

—FRANK AYD, JR., MD, *Baltimore*

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Important Advances in Clinical Medicine

Epitomes of Progress—Obstetrics and Gynecology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Obstetrics and Gynecology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Obstetrics and Gynecology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Obstetrics and Gynecology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Perinatology

On many obstetrical services, the incidence of abnormal or unhealthy newborns has decreased significantly. Whether this is the result of the use of fetal monitoring equipment, better patient surveillance, increased use of cesarean section or some other factor (such as mothers being in better physical health) is unclear. However, it is apparent that many cases of abnormal fetal heart rate patterns in the past represented iatrogenic factors, such as excessive oxytocin infusion, maternal supine position or anesthesia.

Attention is now being directed to detecting poor fetal health in the antenatal period. Adequate maternal diets, rest and avoidance of drugs are receiving added attention. While enthusiasm for the various hormonal indices of fetal well-being is diminishing, more attention is being given to indices of fetal activity and fetal heart rate (FHR) responses. FHR response to uterine contraction is now accorded much importance and beat-to-beat variability is accepted as an indicator of fetal cerebral function.

The usefulness of amniotic fluid analysis to estimate fetal lung maturity is firmly established. The technique of Gluck for lecithin/sphingomyelin (L/S) ratio is accepted as being almost without error for determining in which newborns serious respiratory distress may develop. Unfortunately, the methods for preventing premature labor are not agreed upon, but the various beta-sympathomimetics are successful to a degree while ethyl alcohol has been abandoned in many institutions.

Techniques for diagnosing congenital anomalies in early pregnancy continue to improve. Laboratory tests are now available for specific enzymatic defects. In Europe, great interest is shown in amniotic fluid concentrations of alpha-fetal protein for the detection of open neural tube defects. (The reader is referred to the epitome "Prenatal Screening for Genetic Defects" in this same section.) It is hoped that with the ban on fetal re-

search now revoked, it may soon be possible to sample fetal blood and determine the various hemoglobinopathies *in utero*.

It seems clear that both our patients and pediatric colleagues are taking seriously our claims about our ability to carry out diagnosis *in utero* and provide intensive fetal care. We are expected to deliver only normal and healthy babies.

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Prenatal Screening for Genetic Defects

AN UNBORN FETUS can be monitored *in utero* for various genetic disorders. Intraabdominal amniocentesis, done at 15 to 16 weeks of gestation, provides amniotic fluid for direct study and fetal amniotic fluid cells which can be cultivated for diagnostic cytogenetic and biochemical studies. The diagnostic information so obtained provides couples who are at relatively high risk for conceiving an infant having a genetic disorder with the option of terminating the pregnancy involving an abnormal fetus. The major complication of early amniocentesis is abortion. The frequency (that is, risk) of this occurring as a result of the procedure is 1 percent or less. A potential but as yet unobserved complication of the procedure is isosensitization of an Rh negative woman due to transplacental hemorrhage.

Present indications for prenatal diagnostic studies include the following:

- women over 35 years of age (screen for Down's syndrome and other nondisjunctional diseases—cytogenetic analysis of cultivated fetal cells);
- a previous child with Down's syndrome or other chromosomal abnormality (cytogenetic analysis of cultivated fetal cells);
- either member of a couple known to carry a balanced chromosomal translocation (cytogenetic analysis of cultivated fetal cells);
- a woman who is heterozygous for a deleterious X-linked gene—for example, the gene for Duchenne's muscular dystrophy, hemophilia A or B—(cytogenetic analysis of cultivated fetal cells to determine the sex of the fetus);
- couples at risk for certain hereditary disorders of metabolism—such as galactosemia, maple syrup urine disease, Tay-Sachs disease, Lesch-Nyhan syndrome—(biochemical analysis of cultivated fetal cells);
- a previous child born with a neural tube defect—anencephaly, meningomyelocele and meningocele—(direct analysis of the amniotic fluid for alpha-fetoprotein and ultrasound examination of the fetal head and spine), and
- one member of a couple with a neural tube defect (direct analysis of the amniotic fluid for alpha-fetoprotein and ultrasound examination of the fetal head and spine).

It is important, therefore, for an obstetrician to identify those couples in his care who are at relatively high risk for conceiving a fetus with a genetic disorder amenable to prenatal diagnosis. Genetic counseling centers are available to assist physicians in arranging for these diagnostic studies and to provide counseling for these couples before amniocentesis.

HOWARD CANN, MD

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Abdominal Wall FECG-FHR Monitoring

FETAL HEART RATE (FHR) monitoring has become an integral part in the assessment of fetal well-being. Although direct monitoring with a fetal electrode provides the most precise fetal heart rate data, this technique cannot always be used.

Use of external monitoring with a fetal electrocardiogram (FECG) from the maternal abdominal wall has been reintroduced. The major problem in using an abdominal wall fetal electrocardiogram is its small amplitude which may be submerged or lost in electrical signals emanating from the mother. In order to compensate for this problem, certain "logic" or "censorship" must be used to produce a recognizable fetal heart rate.

Currently three commercial units are available that have received only limited testing. Antepartum monitoring in circumstances that would be considered close to ideal is possible in 80 to 90 percent of patients. Success of the technique will

be greatest when minimal extraneous electrical signals are present. Successful monitoring will depend on factors such as stage of labor, obesity, gestational age and maternal pushing. In general, failures are more frequent as labor progresses.

Although this method has certain limitations, it may prove useful in antepartum fetal heart rate assessment and in the monitoring of early labor.

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Tumor Immunology

IN THE LAST two decades it has become clear that malignant neoplasms are antigenic and as such they evoke an immune response in the host. This immunological reactivity to a tumor antigen suggests that there may be antibodies or cell mediated effectors to the antigens in the peripheral circulation of patients in whom malignancy is present. If either of these components exists, the possibility of assaying blood for their presence would lead to a diagnostic tool for the detection of malignancy. On the other hand, the human organism that musters an immunological response to carcinoma similar to that seen in infectious diseases can be assisted to the extent that this response may be augmented in the form of therapy (immunotherapy).

Tumor associated antigens have been identified in a host of human neoplasms to date. Purification and isolation of these antigens is currently under investigation with the ultimate goal being a sensitive assay such as a radioimmune assay for diagnostic purposes. Immunotherapy is in its infancy and has taken primarily the route of augmentation of the T cell lymphocytes of the peripheral blood. These T cell lymphocytes are the killer cells of the immunological response and their augmentation to date has been nonspecific in the form of generalized stimulants of the immune system such as bacille Calmette Guérin and Corynebacterium parvum. More specific stimulants await discovery and utilization.

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Treatment of Hyaline Membrane Disease—Update

IN THE LAST ten years remarkable progress has been made in understanding the pathogenesis, intensive therapy and prevention of hyaline membrane disease (HMD). The rational approach to therapy includes the anticipation of and attendance at the delivery of an infant at risk to develop HMD, early and intensive therapy with careful and meticulous monitoring of the infant, and recognition and treatment of complications of the disease. Using this intensive care approach, more than 80 percent of infants with HMD should survive. If such an infant weighs 2,000 grams or more, the survival rate should approach 100 percent.

At present the major area of investigation concerns preventing the disorder. Since HMD is a disorder of immaturity, decreasing the incidence of premature birth will effectively decrease the incidence of HMD. We currently recommend that amniocentesis and the measurement of the lecithin-sphingomyelin ratio in amniotic fluid be done before the delivery of any infant by elective induction or elective cesarian section. [It should be noted that amniocentesis per se is not without risk.—Section Ed.] In those cases where maternal or fetal factors necessitate early delivery, such premises may not be well-founded. For those women who go into labor prematurely and in whom there are no indications to the contrary, an attempt to stop labor should be made with an alcohol drip or with isoxsuprine hydrochloride (Vasodilan®). The mother can then be given 12 mg of dexamethasone twice daily for three days in an attempt to mature precociously the production of pulmonary surfactant.

Theoretically, corticosteroids are taken up by receptor sites in the cytosol and nuclei of fetal lung cells, and the production of lecithin by way of choline incorporation pathway is enhanced. Although additional carefully controlled studies are still needed to further evaluate this form of therapy, early data suggest that corticosteroids given to the mother are of value in decreasing the incidence of HMD in her offspring.

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Breast Self-Examination

DESPITE ADVANCES in technology, survival rates for carcinoma of the breast remain almost the same, stage for stage, as they were 35 years ago. The improvement which has been noted in overall survival figures is due primarily to earlier detection of the disease.

At present, mammography is the most effective technique for the early diagnosis of carcinoma of the breast, and the only reliable method for identification of a tumor before a mass is palpable. However, at present, a lack of equipment and trained personnel preclude use of mammography to screen the entire population at risk. Furthermore, the potential oncogenic hazard of repeated breast irradiation may limit the application of this technique in the future.

Since more than 90 percent of breast masses are first noted by women themselves, breast self-examination may be the most practical method for quickly reducing the high mortality rate of breast cancer. However, findings in a recent study carried out by Gallup for the American Cancer Society showed that only 18 percent of adult American women regularly examine their own breasts. The major reasons advanced for this failure to do such examination were fear of cancer, lack of knowledge about the technique and lack of confidence in the ability to recognize an abnormal lump.

The study results also showed the value of a doctor's office as a teaching site for this technique. More than 90 percent of the women taught by the physician or his staff continued self-examination. Of those women taught in other settings, only 14 percent did the examination regularly afterward. Apparently, when this instruction takes place in the doctor's office, women are more highly motivated to learn and apply the information.

Several new approaches to patient instruction have proven to be of great value in the practice setting. Nurses and other members of the office staff have been trained to teach breast self-examination very effectively. Audiovisual materials have been created to reduce the amount of one-to-one teaching time. Simulation models of the breasts have been developed; these are very helpful in building the confidence of women in their ability to find a lump.

Because of the proven effectiveness of teaching in a doctor's office, each physician must find a way to include instruction about breast self-examination in the routine care offered to women patients. At present, this may be the most practical way to quickly lower the mortality rate of carcinoma of the breast.

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Breast Thermography

BREAST THERMOGRAPHY is the pictorial display of the infrared emission of the breast using a heat sensing device. It is an extension of clinical thermometry. It does not diagnose carcinoma but merely records abnormal temperature patterns and differences. Many benign conditions of the breast as well as carcinoma produce abnormal findings on a thermogram. Thermograms are currently being used in conjunction with physical examination and mammography.

When correlated with the presence of carcinoma, investigators have reported a true positive rate from 50 to more than 90 percent. Findings on a thermogram are positive or suspicious in most series in about three fourths of cases of carcinoma of the breast. Both very large and very small malignant tumors may not be detected by the thermogram. Since thermography is sensitive to a wide variety of benign breast disease and cannot distinguish metabolically active benign disease from malignant disease, a false positive rate as high as forty percent will occur if symptomatic women are screened.

The role of thermography is currently being evaluated by the Breast Cancer Detection Demonstration Project (which is sponsored by the American Cancer Society and the National Cancer Institute). It is hoped that it might provide a method of screening patients for mammography, but this is under investigation now and the examination may not be a valid method of patient screening.

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Colposcopic Terminology

COLPOSCOPY HAS GAINED tremendously in popularity in this country during the past ten years and has now become an accepted part of the gynecologist's armamentarium for diagnosis of cervical, vaginal and vulvar neoplastic disease. One of the major problems in colposcopy has been and remains the confusing terminology used in describing colposcopic findings. In the last few years efforts have been made to simplify and clarify this terminology so that now the more commonly used terms are more appropriate. Included in this epitome are the colposcopic terms and some synonyms. The terms without parentheses are the ones most commonly used by colposcopists in the United States. The synonyms and some of the older terminology are enclosed in parentheses. Knowledge of standard terminology is a prerequisite for understanding the literature on the subject and for effective communication among practicing gynecologists, colposcopists and pathologists. The terminology is based on topographic descriptions as viewed through a colposcope with magnification of 10 to 20 times after application of acetic acid to the tissue. Only the term "transformation zone" is defined here because this is the area in which neoplasia occurs most frequently.

Normal Colposcopic Findings

- Original squamous epithelium (mature squamous epithelium)
- Columnar epithelium (plus original squamous epithelium equals original epithelia eversion, erosion, ectropion, ectopy)
- Transformation zone (zone of epidermization or metaplasia) is an area of metaplastic squamous epithelium between the original squamous epithelium and the columnar epithelium

Abnormal Colposcopic Findings

An atypical transformation zone is one in which the metaplastic epithelium has colposcopic features suggestive of neoplasia. These features are:

- White epithelium (fine leukoplakia)
- Punctation (ground, base)
- Leukoplakia (coarse leukoplakia)
- Abnormal blood vessels (adaptive vascular hypertrophy)
- Suspect invasive cancer (coloscopically overt carcinoma)

Other Colposcopic Findings

- Cervicovaginitis (colpitis)
- True erosion (erosio vera)
- Condyloma and papilloma
- Nabothian cysts
- Polyp
- An unsatisfactory examination is one in which the squamocolumnar junction or entire lesion cannot be seen

Numerous references including the ones listed below are available for definitions of the terms included here with detailed descriptions and colpophotographs. The terminology here is accepted and should be employed for clarity and effective communication.

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Xerography of the Breast

XEROGRAPHY OF THE BREAST is a method of study by means of conventional x-rays. The image is created on the surface of a selenium coated plate. Then it is transferred and fused permanently to a specially prepared paper. The images obtained are regarded as highly accurate. In general, there is a higher resolution, a wider latitude and more information than on conventional film mammograms. Many radiologists feel xeromammograms are easier to interpret than film mammograms. This modality of breast examination has been widely used only in the past several years.

Xeromammography has become an excellent method for the detection of occult carcinoma of the breast. As radiologists gain experience with it, the detection of occult carcinoma has been reported as high as 1 percent of all patients examined. In two large series, occult carcinoma represents approximately a third of the cancer found by xerography. Periodic screening of asymptomatic women by xeromammography is being practiced in many communities. At present, it is recommended that the examination, when

carried out on asymptomatic women, be limited to those 35 years of age and older.

The x-ray diagnosis of cancer is usually made because of a mass with or without calcification or because of calcification alone. In occult lesions, precise preoperative localization of the lesion as well as x-ray studies of the specimen are necessary in many cases. X-ray examination should never replace physical examination because, like nearly all medical tests, it is not totally accurate in the detection of cancer. When dominant mass lesions are noted on physical examination, biopsy studies should be done even if findings on a xeromammogram are negative. Nonetheless, xeromammography appears to be an excellent method of diagnosing carcinoma of the breast and, at present, offers the best opportunity for diagnosis of occult carcinoma.

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The Stilbestrol-Adenosis-Carcinoma Syndrome

ALERTED BY A sequence of seven adolescent girls with adenocarcinoma of the vagina seen in 1966 and thereafter, we conducted and reported in 1971 a review study with suitable controls showing an extraordinary association between the lesion and antenatal exposure to diethylstilbestrol (DES).

Rapid dissemination of this fact during the development of a worldwide registry of such cases soon brought to medical attention numbers of girls and young women known to have been similarly exposed. Findings on examination showed that in most there were anomalies of development of the vagina and cervix, including unusually broad cervical erosion (ectropion), cervicovaginal ridges or furrows and extensive patches of vaginal adenosis. Persons exposed before the eighth week of pregnancy are most likely to show teratogenic effects; initiation of DES therapy after 18 weeks have elapsed apparently no longer carries this risk.

In most of the patients with carcinoma there have been coexisting areas of benign adenosis, but transition from one to the other has not yet been shown. The preferred treatment for benign adenosis, therefore, is not yet clearly established. Although it is tempting to recommend mechanical excision or destruction, the extent and distribution of patches of abnormal epithelium detected by colposcopy, Schiller's testing, biopsy or cytology is often such that it would require a formidable procedure and some risk of permanent deformity or stenosis.

Carcinoma has developed in only a small fraction of the women at risk, perhaps in less than one per thousand. The tumors are usually adenocarcinomas of the clear-cell type and can be successfully treated either by surgical procedures or radiation. However, spread by lymphatics is early, and tumors more advanced than stage II (Federation Internationale de Gynecologie et d'Obstetrique [FIGO] classification for cervix or vagina) are likely to have extended to the pelvic nodes. Adequate treatment for cure cannot avoid sacrifice of fertility, but sexual function is well preserved in patients amenable to radical surgical resection with simultaneous replacement of the vagina by a skin graft over a mold.

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Immunology in Fertility

THE PROBLEM of infertility and immunology is multifaceted. Men with sperm agglutinins and oligospermia or azospermia, women with hostile cervical mucous, couples with unexplained infertility and women with early spontaneous abortions may all fall victim to an immune reaction.

It has been known for some time that men with vasectomies or with obstructive duct disease may develop sperm agglutinins and immobilizing antibodies. Findings in recent studies have shown that in a significant percentage of infertile couples, these same antibodies can be found in the sera of the husband and wife as well as in semen.

Tien, in a review article, emphasized the general principles concerning this problem:

- Antisperm antibodies can occur in certain patients.
- Ten to thirty percent of unexplained infertility could be due to antibodies.
- Immobilizing antibodies appear to have a better correlation with infertility than do agglutinating antibodies (though Shulman has other evidence on that point).
- Condom therapy deserves a trial.

However, inconsistencies and contradictions still abound. A recent study was carried out on patients in whom results on postcoital tests were poor, that is, dead or nonmotile sperm being found in otherwise normal cervical mucous. Sixty-four women were studied with the immunofluorescent technique. In 30 percent there was a positive titer. However, there was a positive titer in 26 of 50 women with a known cause for infertility and *normal* findings on postcoital tests. The complexity of the immune reaction is such that diverse reports are to be expected.

Basic and clinical research continues. A study is being carried out to investigate antibody formation within hostile cervical mucous. There are centers now investigating the use of "donor" cervical mucous and homologous insemination for those patients with hostile cervical mucus. Embryos and zygotes have been studied and found to elicit antibody response with destruction of the developing embryo or placenta. Antibodies have been found in uterine fluid which notably reduce survival of embryos in test animals.

When the pieces of the puzzle are finally put together we will not only have a treatment for some patients with unexplained infertility but also possibly the best contraceptive to date.

BENJAMIN KLIGER, MD

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EDITORIALS

A BICENTENNIAL EDITORIAL

The Professional in America Today

THE PROFESSIONS are changing, American society is changing and the relationships between them are changing. The elitism which has been the hallmark of the professional is being seriously challenged, and the field of health care provides good examples of this. The word is about that medicine and health care have come to be too important to be left to health professionals.

These are times of profound social changes. There is a great swing toward egalitarianism. The words in the Declaration of Independence "all men are created equal" are being given the broadest possible interpretation. Under the new interpretation, the phrase seems to mean that all men are just the same—none better, none worse, none different—all equal. Equal justice or equality under the law is one thing, but no two people are ever exactly the same or entirely equal. Any assumption that they are equal and therefore the same is at once anti-intellectual and antibiological. It is anti-intellectual because each person's complement of knowledge and experience is unique and his own, and different from that of every other person's. It is antibiological because, with the exception of identical twins, each person's complement of genes is also unique and different from any other's. For these reasons it seems likely that the great swing toward egalitarianism we are witnessing will create many more problems than it will solve, simply because it is an idea not rooted in any real social or biological truth.

The professional in America today finds not only his elitism but his professionalism being challenged as a part of the swing toward egalitarianism. Again medicine provides a good example. Not too long ago such things as patient care in and out of the hospital, the training of physicians and other health personnel, and research in medical and health science were left largely to the professionals who presumably knew what needed to be done and how to do it. But this is no longer the case. As of today nonprofessionals have an increasing and often a controlling influence on what decisions are made in each of these areas of professional activity. The generally held assumption seems to be that the individual or collective wisdom of consumers or the public is more likely to be correct than is the judgment of professionals.

The professionals have not been entirely faultless. Again particularly in medicine, we became so engrossed in developing and applying new science and new technology that we neglected many of our professional responsibilities to society as a whole. For instance, we have not exercised enough professional leadership in identifying and solving problems of making health care adequately available to all in our society. And in medicine at least, as professionals we still have not found effective enough ways to bring the knowledge and expertise of medicine to bear on a variety of broad social problems pertaining to health and health care. Rather our professions have tended to become ingrown and increasingly absorbed in their own problems, with little time or energy left for addressing the broader social problems that are the root cause of most of their internal problems.

As we look ahead it is clear that things cannot remain as they are. Further change is inevitable. The reality of the social and biological uniqueness of every person and the right of each to an opportunity for personal fulfillment will necessarily displace the unreality of today's egalitarian approach to almost every aspect of life. And the reality of the growing social and technological complexity of American society, with increasing interdependence among human beings, will strengthen rather than weaken the role of professionals, and will greatly increase their number and importance. A new accommodation will therefore become necessary between the professions and the public they serve, with each recognizing a greater responsibility to see to the needs of the other as well as to their own. And it will become more and more evident that professions cannot withdraw from the needs of the society they serve, nor can a complex interdependent society function or thrive without growing use of expert professionals.

Medicine, almost uniquely among the profes-

sions, seems to be in a position to take the lead in what needs to be done now. First we should seek to strengthen the professionals' share in decision making at every level of health care. Second we should develop medicine's knowledge and expertise, not only in the depth of a specialty but also in the breadth of its relationship to the needs and aspirations of society as a whole. And third we should work toward closer cooperation among related professions so as to bring the knowledge and expertise of all health professionals more effectively to bear to help solve the health care problems of today and anticipate those that lie ahead.

—MSMW

Toxic Megacolon

Dr. Rosenberg's discussion of toxic megacolon in this issue of the Journal serves to emphasize several important features of this disorder. Toxic megacolon is not unique to ulcerative colitis but has been observed in typhoid fever, amebic colitis, acute bacillary dysentery and cholera. Although, in this part of the world, the occurrence of toxic megacolon is almost always associated with inflammatory bowel disease, this article provides a reminder that a patient with toxic megacolon has to be studied carefully to eliminate the possibility of causes other than nonspecific inflammatory bowel disease.

Numerous accounts attest to the importance of factors such as hypokalemia, anticholinergics, opiates, cathartics and aerophagia in the development of toxic megacolon. It is important to note that these factors usually do not lead to dilatation of the colon unless extensive and severe inflammatory disease of the colon is present.

The criteria for the recognition of toxic megacolon point out very clearly that it occurs in the severest form of ulcerative colitis. Pancolitis with extensive loss of mucosal surface, inflammation and edema of the colonic wall, and diminished propulsive activity of the colon are the circumstances that lead to toxic megacolon.

Refractory diarrhea, abdominal distension, high pitched bowel sounds, fever, leukocytosis and hypoalbuminemia serve to alert a clinician to the fulminant course of the disease and the potential of megacolon. Plain abdominal films carry no risk to the patient and may show thickening of the colonic wall, extensive ulceration and pseudopolyposis of the mucosa. Use of a barium enema may be an inordinate risk in this phase of ulcerative colitis.

Treatment of ulcerative colitis should be directed primarily toward the acute inflammatory process in the colon and secondarily to the prevention of megacolon. Administration of antibiotics and adrenal cortical steroids, fluids and electrolyte replacement, blood transfusion and parenteral alimentation including hyperalimentation are the measures most effective in treating acute ulcerative colitis. The prevention of megacolon necessitates correction of potassium deficits and the discontinuation of any agent that may adversely affect colonic mobility, such as opiates and anticholinergic drugs. Nasogastric suction should be instituted if colonic dilatation becomes apparent.

Unfortunately, the fulminant nature of ulcerative colitis may not be recognized until the development of toxic megacolon. At this point, not only is the problem one of severity of the disease but, in addition, colonic perforation and sepsis become distinct possibilities. In many if not most patients with this complication of ulcerative colitis, colectomy ultimately will be necessary. The severity of the inflammatory process that led to the megacolon plus the damage to the colon engendered by the colonic dilatation often lead to irreversible changes in the colon. Binder and co-workers, who reviewed 497 cases of toxic megacolon reported in the medical literature from 1955 to 1971, noted that medical management was successful in 28.9 percent of patients.[1] On the other hand, surgical treatment of toxic megacolon with perforation has a mortality rate of 51.2 percent. If a clinician appreciates the possible risk of perforation and sepsis, and the increasing risk of these complications with the passage of time, then the lesson is clear. The potential of remission of the megacolon or the likelihood of improvement in the patient's status before surgical operation indicates a brief trial of medical management. Most authors advocate a time limit in the medical management of toxic megacolon. A significant reduction in colonic perforation and mortality has been achieved by earlier operation in these patients. However, if there is no attempt at conservative medical management before operation, a significant number of patients will undergo colectomy needlessly. More important than the time interval before surgical operation is the intensity and accuracy of obser-

vation of a patient's response to the medical program for toxic megacolon. The decision to operate or persevere in medical management should be based on the response to therapy rather than an arbitrary time limit.

Frequent clinical and x-ray evaluations of the colonic dilatation, leukocyte counts and vital signs enable a clinician to monitor response to therapy. If within 24 to 48 hours no improvement is noted (that is, decreasing diameter of the dilated colon, reduction in fever and reduction in the leukocyte count and tachycardia) colectomy is indicated. If the colon continues to dilate, in spite of adequate medical management including nasogastric decompression, colectomy should be carried out as soon as possible.

The morbidity and mortality of fulminant ulcerative colitis and toxic megacolon remain excessively high.[2] Recognition of the importance of early diagnosis of the fulminant disease, of the various factors which contribute to megacolon, and of the necessity for effective and appropriate therapy should help to improve this.

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Regulating Acupuncture in Nevada

ELSEWHERE in this issue of the JOURNAL, Dr. William Edwards has presented a report on the current status of acupuncture and Oriental medicine in the state of Nevada. The article well describes what progress has been made since an earlier article appeared in these pages in June 1974.

Acupuncture in Nevada has not turned out to be the pot of gold that was envisioned by its strongest proponents, those who played a major part in getting the necessary legislation quickly passed by the Nevada State Legislature. Acupuncture is far from emulating the historic mother lode in silver and gold strikes of Virginia City, or the modern gambling take of "Glitter Gulch" in Las Vegas.

As patients found that acupuncture was not the panacea it had been loudly proclaimed to be in the lobbying, and that its cost was far from modest, the rush quickly tapered off. Also, it soon became evident that complications such as accidental pneumothorax, hematomas and persistently painful puncture wounds really happened.

It is to the credit of our governor and the Board of Oriental Medicine appointed by him that both have acted responsibly to prevent the development of a real racket. This might have occurred even without violation of the loose and incomplete law that the Legislature rushed through. There are several possible loopholes and faults in the law that the Legislature has not corrected, but the appointed Board of Oriental Medicine has formulated rules so that these could not be exploited. A less conscientious board might well have permitted a great deal of public exploitation for private gain.

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Manpower Necessary to Perform Quality Echocardiography

IN THE current issue of the JOURNAL there is an excellent review of the uses of echocardiography in congenital heart disease by Drs. Moss, Gussoni and Isabel-Jones. Echocardiography, which is the use of ultrasound to record the location and motion of cardiac structures in a noninvasive manner, is playing an increasingly important role in the diagnosis of various heart diseases. As indicated in this article, one of the major uses for this diagnostic tool is in the management of patients with congenital heart disease. While reading this article, I was impressed with the amount of technical detail mentioned by the authors. It seemed as though they were constantly reminding the reader of possible technical difficulties and of the care with which the examination had to be carried out. These comments are not only pertinent and important but I would like to enlarge on them.

Echocardiography is frequently described as simple. As far as the patient is concerned, this may be true. There is virtually no discomfort for the patient, and as best we can determine there is absolutely no hazard from the examination. On

the other hand the amount of skill and expertise necessary to obtain and interpret an echocardiogram is increasing constantly. Not too many years ago the mere identification of the anterior leaflet of the mitral valve was sufficient to call oneself an echocardiographer. Now we not only record echoes from many more areas of the heart than the mitral valve, we might even ask which echo from the anterior leaflet of the mitral valve did one wish to record. As with practically everything else, time and experience make nothing simpler, only more complicated. At present, echocardiography has become a very sophisticated diagnostic technique which requires a great deal of knowledge and skill in both the examination and the interpretation. Merely wanting echocardiography to "make the diagnosis of mitral stenosis and pericardial effusion" can no longer be justified. As indicated in the article in this issue of the JOURNAL, echocardiography can do much more than this and clinicians will expect this added information from their echocardiographic laboratories.

The question as to how one makes certain that this type of echocardiographic expertise is available for those patients and clinicians who might benefit from this diagnostic tool, points out a serious problem of education and training in echocardiography. This problem is probably the single most important one facing echocardiography. It is obvious that with any new diagnostic procedure unless it is in the hands of people who are well trained and conscientious, the technique will undoubtedly be abused or used improperly, and the entire technique could fall into disrepute.

The enthusiasm and popularity of echocardiography has been too rapid for an orderly growth and development of the field. So many people want to do the examination or have the technique available that the people in the field can not possibly train all of those who want to develop these skills. In the early days of echocardiography it was merely a matter of visiting an active echocardiographic laboratory for a few weeks or less to learn all that was known about the examination. A laboratory might have only one or two visitors at a time and it was relatively easy to give personal attention to these trainees. Now we have the double problem of having too much to teach and far too many persons wanting this instruction. This is a serious problem because some people are obviously not waiting for such instruction or are taking very superficial courses as their basis for beginning a laboratory.

Echocardiography has certainly become as sophisticated a technique as cardiac catheterization. The examination may not have the same hazards with respect to the patient; however, the technical skills that one must learn in manipulating a transducer are very similar to those necessary in manipulating catheters. Certainly the interpretation of an echocardiogram can clearly be as sophisticated as the interpretation of hemodynamic or angiographic data. When an institution wants to set up a catheterization laboratory, ordinarily a person who is formally trained in the various catheterization techniques would be sought, usually as part of a fellowship program. I believe that we are fast approaching a similar situation with echocardiography. There are many excellent echocardiographic laboratories in major teaching centers that are producing well trained echocardiographers who have received closely supervised instruction. Again this instruction is primarily a part of a cardiology fellowship program. It would be almost impossible for any practicing physician currently to obtain this type of training. Thus if an institution wanted to start an echocardiographic laboratory, one of these formally trained physicians who has the endorsement of the physician in charge of his education should probably be sought to run that laboratory.

Although the supply of such trained echocardiographers should increase significantly in the next few years, many institutions and physicians do not want to wait to obtain such a person, and they are trying to obtain echocardiographic training for practicing physicians. This is becoming an increasingly difficult chore. I know of no institution which will provide any lengthy or intensive training in echocardiography for practicing physicians. Such a course would require a minimum of a three-month experience at an institution in which the trainee would do four to five echocardiograms a day and interpret an even larger number under the direct supervision of an accomplished echocardiographer. This is essentially the experience that cardiology fellows obtain at present. Even if physicians could afford to give up three months of their time, it is doubtful that many laboratories would permit such use of their institution because of their commitment to their own cardiology fellows.

The only type of training that is available to practicing physicians who want to do echocardiography is some short workshop session in which they learn the basic principles of echocardiog-

raphy. These courses usually last less than a week and the students examine eight to ten patients during that time. There is absolutely no possibility that one can become a trained echocardiographer with that type of experience. If, on the other hand, such a person is willing to continue his self-education after returning to his home institution, then it may be possible to gradually gain more experience and more confidence with the technique. Because there is no one available for critical evaluation of the student's examinations and interpretation, the length of time necessary to become proficient will naturally take longer than with a formal program. Obviously some persons learn faster than others, but it is highly unlikely that one could become a competent echocardiographer in less than 6 to 12 months with this type of training experience. As more and more details need to be learned with this technique, this largely self-educational approach is becoming less and less feasible. So in the very near future there should be a decreasing number of self-trained physicians entering the field and an increasing reliance on physicians who are formally trained.

The problem of education and training is not limited to physicians. It is well recognized that nonphysicians can make excellent echocardiographic technicians. Since the examination itself is not hazardous to the patient, technologists can do the echocardiographic examination and frequently can do the examinations better than physicians. It should be obvious that the type of technician doing this examination must be well versed in cardiac anatomy, physiology and pathology. This type of examination is not similar to taking an electrocardiogram or chest roentgenogram. One does not merely place leads at various areas of the chest or put the patient against a roentgenograph and push a button or turn the dial to the appropriate electrocardiographic leads. An echocardiographic examination is a very customized procedure. The examination of each patient is slightly different. The direction of the ultrasonic beam has to be carefully adjusted in order to record the desired echocardiographic information. An echocardiographic technician knows that the transducer is properly directed when he can identify the structures that he is recording on the oscilloscope. The better the cardiological background of this person, the better prepared he will be to understand as well as recognize an abnormal situation. As pointed out in the article written by Dr. Moss and associates, the technical details are even more important in congenital heart disease—especially in patients in whom pronounced distorted cardiac anatomy is present. Therefore it is obvious that any technician doing echocardiography, especially the examination of a complex congenital problem, must be well versed in normal as well as abnormal cardiac anatomy and physiology.

The training of such echocardiographic technicians is currently more of a problem than trying to produce a supply of physicians educated in echocardiography. There are very few, if any, formal training programs producing echocardiographic technicians. There are several technical training programs over the country where echocardiography is taught along with other diagnostic ultrasound procedures. These training programs are primarily geared to put out technologists who have a superficial knowledge of all ultrasonic procedures. To date such programs have been grossly inadequate with respect to echocardiography. In addition these programs have not prepared these people to function in a cardiovascular laboratory where they must also be knowledgeable in other cardiological tests such as phonocardiography and pulse tracings. There are a few schools in which cardiovascular or cardiopulmonary technology is taught. Some of these schools apparently have training in echocardiography; however, the quality of training in these programs has yet to be determined. Until now most of the echocardiographic technologists have been trained by the individual physicians with whom they work. This on-the-job training has been highly successful in many situations but it is obviously not satisfactory to meet the national need for these people. Thus some type of formal training for technologists who can carry out high quality echocardiography must be devised soon.

There is no question that without an adequate supply of highly skilled, well trained physicians and technologists, clinicians and patients will not be able to receive the full benefit of some of the echocardiographic diagnoses mentioned by Dr. Moss and his associates. This problem is being recognized by an increasing number of echocardiographers and it is to be hoped that soon some practical solutions will be forthcoming.

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CASE REPORTS

Refer to: Jordan GW, Bauer R, Wong GA, et al: Staphylococcal myositis in a compromised host—Successful treatment with the synergistic combination of nafcillin and gentamicin. West J Med 124:140-143, Feb 1976

Staphylococcal Myositis in a Compromised Host

Successful Treatment with the Synergistic Combination of Nafcillin and Gentamicin

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HEMATOLOGIC MALIGNANCIES and their treatment result in hypersusceptibility to many infectious agents as a consequence of suppression of normal host defense mechanisms. A severe staphylococcal infection, resembling tropical myositis, developed in a patient with myelomonocytic leukemia. Recovery followed treatment with nafcillin and gentamicin, a combination shown to be synergistic against the Staphylococcus aureus isolated from this patient.

Report of a Case

A 30-year-old black man was admitted to the University of California (Davis)-Sacramento Medical Center (UCD-SMC) with a one day history of bilateral thigh and arm pain, and fever. One year previously, he had been seen at UCD-SMC because of malaise, fatigue and dyspnea on exertion. Hepatosplenomegaly and pancytopenia were found; findings on bone marrow biopsy, lymph node biopsy and ferrokinetic studies were consistent with a myeloproliferative disorder, but of unknown type. Subsequently, a diagnosis of myelomonocytic leukemia was made. Hemoglobin type was AA, serum immunoglobulin levels were normal, and reactions to both intermediate purified protein derivative (PPD) and mumps skin tests were negative. The patient was treated with prednisone, and a dose of 100 mg every other day was continued to the current admission. During this interval, the leukocyte counts were consistently low, ranging between 1,200 and 2,100 cells per cu mm.

On physical examination at admission to UCD-SMC, the patient appeared to be in a toxic condition. Temperature was 102°F (38.9°C), pulse rate was 150 beats per minute and blood pressure was 100/60 mm of mercury. Both thighs and arms were swollen, erythematous, warm and tender. The skin was intact and there was no evidence of peripheral embolization. Scleral icterus, a grade 2/6 systolic ejection murmur along the left sternal border and hepatosplenomegaly were present. Right lower quadrant tenderness and guarding were present; however, bowel sounds were normal. The hematocrit reading was 36; of 1,600 leukocytes per cu mm, 85 percent were lymphocytes and 15 percent were polymorphonuclear leukocytes. There were 25,000 platelets per cu mm. The creatine phosphokinase value was 2,000 units; the serum aldolase level was normal, and myoglobinuria was not detected. Six blood cultures and a culture of serosanguineous exudate aspirated from the left thigh yielded staphylococcus aureus which was shown to be resistant to penicillin G *in vitro*.

Treatment was begun with 250 mg of nafcillin per kg of body weight per day injected intravenously as six equal portions (3 gm) every four hours and 5 mg of gentamicin per kg of body weight per day injected intravenously as six equal

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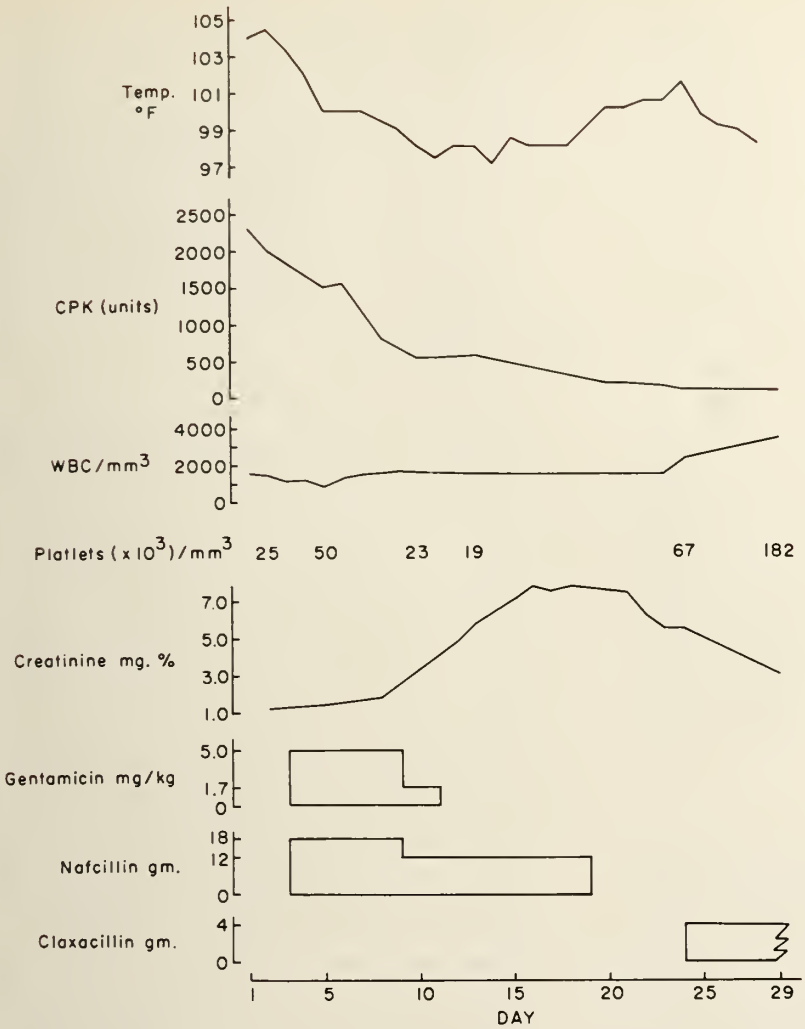

Figure 1.—Clinical course of the patient while at the Sacramento Medical Center. CPK=creatine phosphokinase.

portions (60 mg) every four hours. After six days, the dose of gentamicin was reduced to 1.7 mg per kg of body weight per day given intravenously as six equal portions (20 mg) every four hours. Because of a progressive rise in the serum creatinine (Figure 1), and because there had been resolution of the abdominal pain, muscle swelling, tenderness and fever, the gentamicin was discontinued and the nafcillin dosage was reduced to 2 gm every four hours for the remaining ten days of therapy. Hydrocortisone was given initially at a dose of 50 mg intravenously every six hours and was continued for 17 days at which time prednisone therapy was resumed. Fever returned three days after administration of nafcillin was stopped; therapy with cloxacillin—55 mg per kg of body weight per day given perorally as four equal portions (1 gram) every six hours—resulted in defervescence within two days. Cloxacillin treatment was terminated after ten days.

Antimicrobic Synergy

The bactericidal activity of different combinations of nafcillin and gentamicin against the strain of Staphylococcus aureus in this case was determined as described by Barry and Sabath.[1] Briefly, serial dilutions of each drug were prepared in Mueller-Hinton broth and combined in a two dimensional array. Each tube was inoculated with 10^5 colony forming units (CFU) per ml. After 18 hours of incubation, 10 percent of the volume of each tube without visible growth was subcultured on drug-free blood agar plates and the number of survivors calculated. Concentrations which resulted in a 99.9 percent reduction of viable units were accepted as minimal lethal concentrations (MLC) which are plotted as an isobologram (Figure 2). The straight line connecting the MLC for gentamicin alone with the MLC for nafcillin alone represents the MLC's ex-

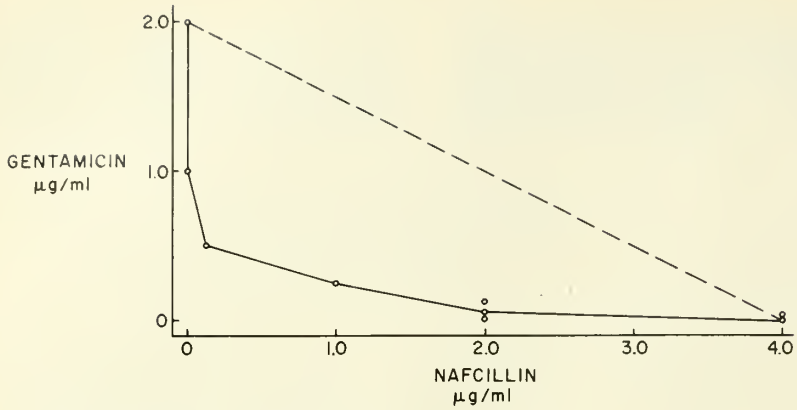

Figure 2.—Isobologram demonstrating the syngergistic effects of nafcillin and gentamicin in achieving a 99.9 percent reduction of viable Staphylococcus aureus. The dashed line shows the relationship expected for additive drug effects.

pected if these drugs were simply additive in effect. Because the MLC's of the combinations were in fact less than would be expected from addition, the combined action was synergistic. For example, a 99.9 percent bactericidal effect required 2 micrograms (µg) per ml of gentamicin or 4 µg per ml of nafcillin acting alone but was achieved with only 0.5 µg per ml of gentamicin and 0.125 µg per ml of nafcillin acting in combination.

Discussion

The manifestations of the illness in this case were strikingly similar to the clinical features of tropical myositis.[2-4] The distribution of acute inflammation to the large muscle groups of the thigh and upper arm in a febrile patient is characteristic and provided an important clue to the cause, and hence to treatment. Involvement of the right iliopsoas muscle was indicated by right lower quadrant pain and the tendency for the patient to lie with the right thigh partially flexed. This is a well described feature of tropical myositis and should not be confused with intraabdominal causes of right lower quadrant pain. The conditions that predispose to the development of the tropical disease are not clear although malnutrition, parasitic disease and trauma have been mentioned. "Tropical" pyomyositis, without serious underlying disease, may be seen in North America in persons who have recently arrived from tropical areas.[5] In the present case, it seems clear that the underlying hematologic malignancy and leukopenia were responsible for the fulminant myositis and bacteremia. A variety of clinical conditions that result in impaired host defenses have been associated with staphylococcal bacteremia; however, myositis has not been described as a clinical feature in these patents.[6]

Although the effect of antimicrobics on bacteria *in vitro* may be dramatic, the results of treatment are often decisively influenced by host defenses. This can be seen in diseases which involve local impairment of defenses, as in bacterial endocarditis. Mediators of host resistance either cannot reach the site of infection or are prevented from bactericidal action by the local environment, and the antimicrobics used in therapy must kill the infecting bacteria for success in treatment. General impairment of defenses, as in patients with congenital immunological deficiencies or chronic granulomatous disease, also renders successful treatment with antimicrobics more difficult. This is also true in patients with the acquired deficiencies which occur in myeloma, lymphoma and leukemia, and as a result of therapy with immunosuppressive drugs or with ionizing radiation. Despite the development of potentially bactericidal antimicrobics, the treatment of infections in granulocytopenic patients is often ineffective.[7] Unfortunately, there is little information on the extent to which antimicrobic treatment must be augmented when there is a particular defect in host defenses.

With some microorganisms the bactericidal effects of one antimicrobic are greatly enhanced in the presence of a second antimicrobic with a different mechanism of action. The classical example of this phenomenon is the synergistic action of penicillin and streptomycin against strains of enterococci;[8] this combination has been successfully applied to the treatment of enterococcal endocarditis.[9] Other examples of antimicrobic synergy are known,[10] including evidence for a synergistic effect *in vivo* of a penicillin and an aminocyclitol against Staphylococcus aureus.[11,12] The combination of penicillin G and gentamicin was found to be more effective than either anti-

microbic alone in the treatment of experimental staphylococcal infections in mice.[13] Because it was necessary to obtain the greatest possible bactericidal effect in this critically ill patient with leukopenia, a combination of nafcillin and gentamicin was used initially. As shown in Figure 2, the minimum lethal concentrations of combinations of these two antimicrobics were less than predicted by additive effects, confirming previous results with this combination against S. aureus.[14] It should be pointed out that some antimicrobic combinations have merely additive effects while others may be antagonistic.[15] For example, a deleterious clinical effect was shown in the treatment of pneumococcal meningitis with the combination of penicillin and chlortetracycline.[16]

A gratifying response to treatment was obtained in this case as shown in Figure 1. During the first week, the patient's temperature returned to normal and his general condition improved notably. There was extensive destruction of muscle, as evidenced by the serum creatinine phosphokinase level; although the concentration of the enzyme decreased rapidly, it did not become normal until the third week. Abscess formation requiring drainage, a characteristic feature of pyomyositis, did not occur in this patient with leukopenia. The creatinine clearance declined with a progressive rise in the serum creatinine level. Several factors may have been responsible.

It might be suspected that myoglobin released from damaged muscle could contribute to the renal impairment; however, the urine sediment was normal and myoglobinuria was not detected. Myoglobin has not been detected in the urine of patients with tropical myositis; however, tubular necrosis with oliguria does occur and has been related to the presence of dehydration and shock.[17] In our patient, hypotension and tachycardia were present for several days and it is likely that some degree of renal ischemia as well as gentamicin toxicity resulted in impaired renal function. Fever returned during the last week in hospital at which time a good response was obtained to orally administered cloxacillin, although S. aureus was not isolated again from cultures of the blood.

Clinical situations have been described in which impaired host defenses compromise the outcome despite treatment with antimicrobics. In such patients, it is necessary to obtain maximum bactericidal effects for prolonged periods to effect a cure. Although our patient might have recovered with use of nafcillin alone, the presence of leukemia with leukopenia and a rapidly progressing staphylococcal infection, prompted vigorous application of a potentially synergistic combination of antimicrobics. Rational combinations of antimicrobics may have a place in therapy when there is severe impairment of host defenses.

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Pneumopericardium and Pneumothorax Complicating Bronchogenic Carcinoma

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PNEUMOPERICARDIUM AND PNEUMOTHORAX are extremely rare complications of bronchogenic carcinoma. We present a man with far-advanced carcinoma of the lung in whom a pneumothorax first developed, then a pneumopericardium during the course of illness.

Report of a Case

A 64-year-old man, a security guard, was admitted to the Los Angeles County, University of Southern California Medical Center on June 3, 1974 with a three month history of right-sided chest pain, progressive dyspnea, productive cough, night sweats, weakness and a weight loss of 50 pounds. Findings on a roentgenogram of the chest taken at an outside hospital two months before admission had shown a lesion in the right lung. On bronchoscopy, carried out two weeks before admission, no abnormalities were noted. The patient had been smoking one to two packages of cigarettes for 50 years.

On admission, blood pressure was 108/76, pulse 70, respiration 18 and temperature 36.7°C (98°F). The patient was cachectic but in no acute distress. There were decreased expansion, vocal fremitus and breath sounds on the right side. On percussion of the right side of chest, tenderness and flatness were noted. Heart sounds were within normal limits. Results on the rest of the physical examination were unremarkable. Hemoglobin was 12.5 grams per 100 ml, and leukocyte count 4,900 with a normal differential. Serum calcium was 10.3 mg per 100 ml and albumin was 3.2 grams per 100 ml. On a roentgenogram of the chest, bullous changes were seen as well as a pleural effusion on the right side, with the suggestion of a mass in the right lower lobe (Figure 1). Thoracentesis yielded 750 ml of amber colored fluid with a specific gravity of 1.016 and protein of 3.9 grams per 100 ml. Many lymphocytes were seen but there were no malignant cells. Tuberculin, coccidioidin and histoplasmin skin tests gave negative results after 48 hours. Results of multiple sputa studies for acid-fast bacilli were negative.

On fiberoptic bronchoscopy, carried out on June 13, an infiltrative lesion was seen narrowing the right main stem bronchus. Although an attempt at biopsy of the lesion was unsuccessful, the next day the patient expectorated a piece of tissue, which on microscopic examination indicated keratinizing squamous cell carcinoma. On a roentgenogram of the chest taken 12 days later (June 25), the pleural effusion was seen to have recurred (Figure 2). Other than the previously existing bullae, there was no evidence of air in the chest cavity. Radiotherapy with cobalt-60 was begun. The subsequent course of the patient was complicated by hypoalbuminemia, hyponatremia,

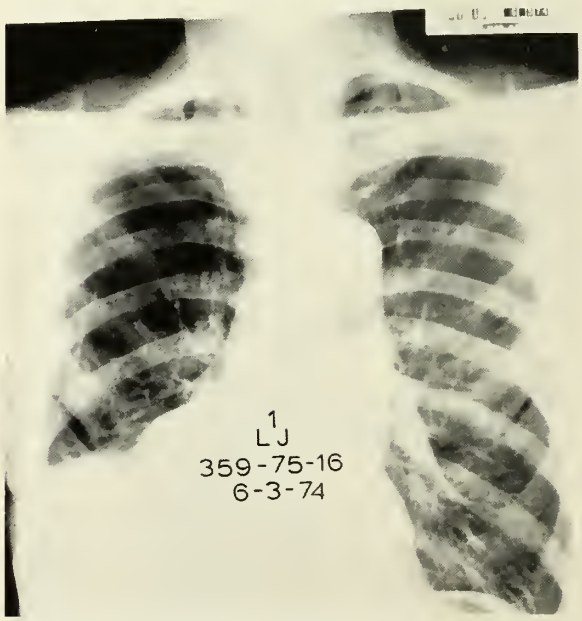

Figure 1.—Admission roentgenogram of chest showing pleural effusion and suggestion of mass in right lower lobe. Note extensive bullous changes at both apices.

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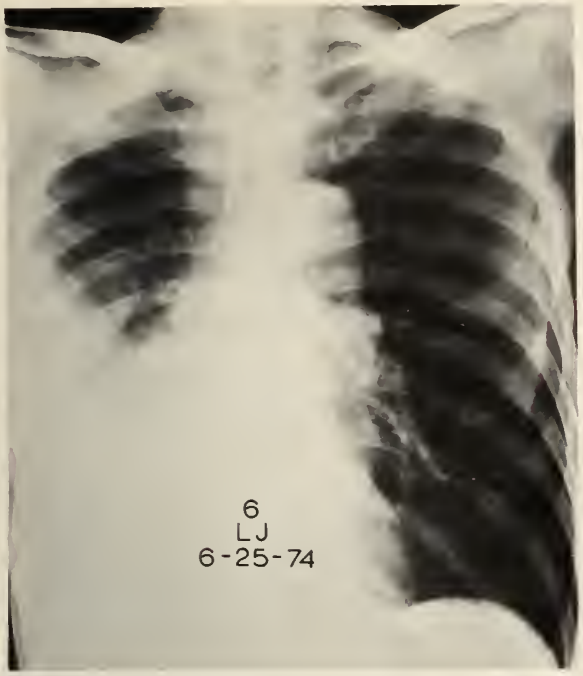

Figure 2.—Roentgenogram of chest on 23rd hospital day showing reaccumulation of fluid following thoracentesis. Note absence of air in chest cavity and pericardium.

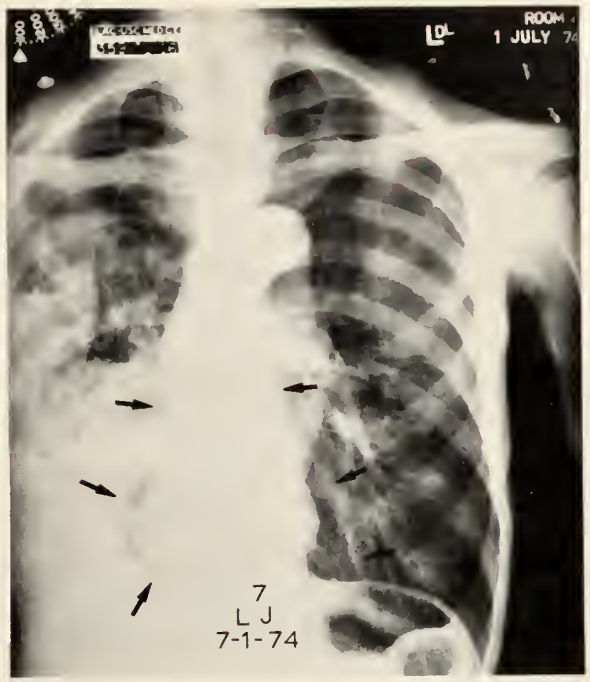

Figure 3.—Roentgenogram of chest on 28th hospital day showing pneumopericardium (arrows). Note also small pneumothorax at right upper lung field.

hypercalcemia (serum calcium rose to 12.5 mg per 100 ml), confusion and a right facial hemiparesis. Saline solutions, albumin, oxygen (given nasally) and high calorie supplements were administered.

On July 1, findings on a roentgenogram of the chest showed the presence of a small pneumothorax as well as a pneumopericardium (Figure 3). The patient's blood pressure fell to 80/60 and the pulse rate rose to 116, although no signs of shock were seen. On auscultation of the heart, a grating, swishing sound coincident with heart sounds ("water-wheel murmur") was noted. The pneumopericardium was noted to persist until the pleural effusion reaccumulated. Although there was temporary improvement of both subjective and objective clinical status, the patient's course was one of progressive deterioration and he died on July 24, the 51st hospital day. Autopsy was not carried out.

Discussion

Malignant tumors of the lung have been reported to be associated with pneumothorax and pneumomediastinum, but it is of interest that most of these have occurred with metastatic bone sarcomas.[1,2] Heimlich and Rubin[3] and Citron[4] reported several cases in which a primary bronchial carcinoma was associated with spontaneous pneumothoraces.

Although pneumopericardium in association with primary bronchial carcinoma is a rare event, it has been seen as a complication more commonly with other problems. Meyer[5] lists trauma, perforated visci, systemic infections (rarely with gas forming organisms), perforation of malignant tumors into the pericardium and primary suppurative pericarditis as the major causes of this entity. Although trauma is the most common cause, perforated esophageal and peptic ulcerations have particularly occupied the interest of thoracic surgeons because of their unique anatomic locations as well as because of their grim prognosis.[6-9]

Until recently, the only malignant tumors reported in association with pneumopericardium have been esophageal and, rarely, gastric carcinoma.[10,11] Harris and Kostiner[12] were the first to report a case of bronchogenic carcinoma involving a pneumopericardium. Ours is therefore the second such case reported in the English language literature.

The signs and symptoms are usually characteristic in pneumopericardium. Unless the patient

had prior reason for chest discomfort (as ours did), there is usually a sudden onset of precordial pain, dyspnea, cyanosis and venous distention. There may be increased tympani as well as widening of the area of cardiac dullness. A loud splashing sound similar to the one heard in our patient can be auscultated in synchrony with systole, the so-called "water-wheel murmur."[7] On a roentgenogram of the chest, the pericardial cavity is found to be dilated more to the left than to the right.[6,12] The air is cut off superiorly by the aortic arch. Because of the hollow pericardial space, cardiac movements are particularly active and this is readily detectable on fluoroscopy.[6]

These features help to distinguish this entity from pneumomediastinum (mediastinal emphysema). In the latter, symptoms are those of severe substernal chest pain, occasionally radiating to the back, neck or shoulders. However, there are usually no constitutional symptoms, such as those suggestive of decreased cardiac output.[13] Auscultatory findings show a "Hamman's crunch" which has a more bubbling, popping or crackling sound than that which is heard with a pneumopericardium. This is often accompanied by subcutaneous crepitation. Pneumothoraces have been observed with mediastinal emphysema and it is thought they are due to the escape of interstitial air into the pleural space through the mediastinum.[13] Contrary to findings with a pneumopericardium, a roentgenogram in pneumomediastinum shows air in the mediastinal tissues *above* the level of the aortic root. Often air is seen running into the neck and above the clavicles.

The reasons for the appearance of air within the pericardium may be several:

- Direct invasion of the tumor into the pericardium with perforation due to necrosis, thus creating a bronchopericardial fistula.
- Possible trauma to the necrotic tumor by bronchoscopy. This is unlikely in our case in view of the fact that the pneumopericardium appeared more than two weeks after the bronchoscopy was carried out. Indeed, findings on a roentgenogram of the chest taken 12 days following bronchoscopy failed to show air in the pericardium.
- Another possibility is an indirect mechanism of the tumor. Lobar collapse by tumor and effusion of part of the right lung already involved by bullous emphysema could lead to overexpansion with rupture of a bulla into the pericardium (through a necrotic focus). This mechanism has been postulated by Citron as a possible cause of pneumothorax in bronchogenic carcinoma.[4] It is of interest that in our patient bullous disease was also present at the time of diagnosis, and a small pneumothorax was noted at the time the pneumopericardium developed.

We are unaware of any instance in which a direct causal relationship between pneumothorax and pneumopericardium has been shown.

Unfortunately, the lack of an autopsy prevented us from determining the exact cause of the findings in this case.

Harris and Kostiner's patient with pneumopericardium died rapidly, presumably because of cardiovascular collapse.[12] Since in our patient there was no associated hemopericardium or pyopericardium, pericardial tamponade was not seen and this aspect of the disease probably did not contribute to his death. Pneumopericardium is, however, a potentially fatal condition. It must be treated aggressively with a combined medical-surgical approach.[5,7-9] This involves pericardiocentesis, appropriate antimicrobial therapy and, when the patient's condition allows, surgical drainage.

Summary

Pneumopericardium and pneumothorax associated with primary bronchial carcinoma are extremely rare findings. We present a patient in whom such an entity developed during the course of illness. Characteristic physical and roentgenographic findings were present. The pathogenesis, clinical presentation and course of this disease are discussed.

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Refer to: Shaub M, Gordonson J, Sargent EN: Extrapleural lipoma. West J Med 124:147-149, Feb 1976

Extrapleural Lipoma

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LIPOMAS ARE THE most common type of primary benign neoplasm of the soft tissues of the chest wall. Intrathoracic lipomas are quite rare and are usually found in the mediastinum.[1,2] Extrapleural lipomas are even more uncommon, and the purpose of this report is to present four cases of lipomas in the extrapleural space.

Reports of Cases

CASE 1. The patient was a 48-year-old asymptomatic Mexican-American man. On a routine radiograph of the chest a typical extrapleural mass measuring 2 by 5 cm, with a convex medial border and tapering margins, was seen in the right upper posterior thorax (Figure 1). There were no associated rib erosions. At thoracotomy, a fatty extrapleural mass was found which tapered as it entered the intercostal space. Exploration of the intercostal space proved the mass to be entirely within the thoracic cavity. Following total removal of the lipoma, the patient had an uneventful postoperative course.

CASE 2. The patient was a 33-year-old asymptomatic Caucasian woman. On a routine radiograph of the chest a mass measuring approximately 5 cm with a convex lateral border overlying the cardiac shadow, was noted located in the right anterior cardiophrenic area (Figure 2). The preoperative diagnosis was a pericardial cyst, but at thoracotomy a large lipoma measuring approximately 10 by 15 cm was found. It projected inferiorly from the eighth intercostal space in the midline near the anterior attachment of the diaphragm and it was freely movable upon the pericardial surface. The postoperative course was uneventful.

CASE 3. The patient was a 31-year-old asymptomatic black man. Findings on a routine radiograph of the chest showed a typical extrapleural mass measuring 2 by 5 cm, smoothly outlined with a convex medial border and tapering margins, located in the anterior portion of the left posterior thorax (Figure 3). There were no rib erosions. Diagnosis of this lesion was made by needle aspiration biopsy which yielded typical

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Figure 1.—(Case 1) **Left,** posteroanterior radiograph of the chest showing a 2 by 5 cm extrapleural mass within the right upper thoracic cage. **Right,** right anterior oblique view showing extrapleural characteristics, that is, tapering margins and smooth convex border, best seen in profile in the right upper posterior hemithorax.

fatty tissue cells. The patient refused a thoracotomy and the lesion did not change in size during a recent 13-month follow-up.

CASE 4. The patient was a 58-year-old black woman with a left breast mass. Findings on routine radiograph of the chest again showed a typical extrapleural mass measuring approximately 3 by 4 cm, smoothly outlined, with a convex medial border and tapered margins, located in the right upper posterior thorax. There was no evidence of any rib erosion (Figure 4). On left radical mastectomy for the breast mass, adeno-

Figure 2.—(Case 2) **Left,** posteroanterior radiograph of the chest showing a 5 cm extrapleural mass overlying the right cardiac border. **Right,** lateral view of the chest showing location in the anterior portion of the mediastinum.

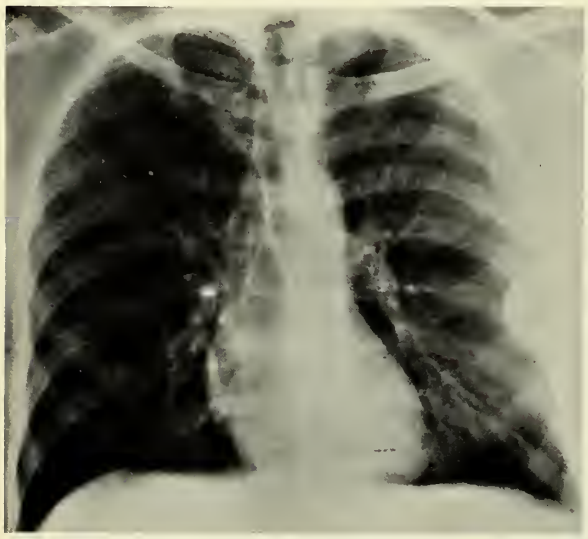

Figure 3.—(Case 3) Posteroanterior radiograph of the chest showing a 2 by 5 cm extrapleural mass with smooth border and tapering margins in the left hemithorax.

Figure 4.—(Case 4) Right anterior oblique view showing typical tapering margins of an extrapleural mass located in the right posterior hemithorax.

carcinoma was seen. Needle aspiration biopsy of the extrapleural mass showed it to contain fatty tissue cells. Thoracotomy was refused and there was no change following a recent observation after 17 months.

Discussion

Thoracic lipomas have been classified into three groups.[4-6]

In the first group, an intrathoracic and extrathoracic element is connected by a narrowed isthmus of tissue. This usually extends through an intercostal space, but in rare instances the tumor may extend through a defect in the sternum. These transmural tumors have been called the "hourglass" or "dumbbell" types.

In the second group, a tumor originating in the mediastinum extends up into the neck. This is called the cervicomediastinal type, with part of the tumor in the upper mediastinum and part in the base of the neck. Occasionally, tumors in the anterior-superior mediastinum may originate in the thymus gland where they are called thymolipomas.

In the third group, the tumor is entirely intrathoracic and this is called a subpleural lipoma. It may occur in a costal diaphragmatic location or mediastinal location. They are more frequent within the mediastinum and of the 61 cases of purely intrathoracic lipomas reported by Seltzer, 46 cases were exclusively mediastinal.

Pathologically, intrathoracic lipomas are similar to lipomas in other locations. They are composed of lobules of normal adult fat, with or without a capsule.[6] Most patients with intrathoracic lipomas are asymptomatic[7] and the tumors are discovered on routine roentgenograms of the chest. Intrathoracic lipomas generally vary in size from 3 to 10 cm.[6] Occasionally, they may become very massive, for instance Leopold reported a case in which a lipoma weighed 17.5 pounds.[8] They have been reported in patients ranging in age from 11 months to 72 years.[6,9]

The possibility of an intrathoracic lipoma should be considered in the differential radiographic diagnosis of any extrapleural mass. When the tumor occurs in a mediastinal or subcostal location, it will have the characteristic appearance of an extrapleural lesion with the following radiographic features. The margin will be smooth and sharply convex, usually with tapering edges forming an obtuse angle. There is usually no evidence of rib erosion or destructive osseous changes. The fatty nature is not readily apparent when it is contrasted with the lung parenchyma that it displaces. However, when the tumor is of the "hourglass" type, the fatty nature may be apparent when contrasted with the water density of the adjacent soft tissues of the chest wall. In this type of tumor, rib erosions may be present.[1,9] If the extrathoracic component is clinically palpable, this aids in the diagnosis of the lesion.

Gramiak and Koerner[10] reported two cases of subpleural lipoma in which the shape of the lesion changed during respiration. Heuer[3] described a peripheral radiolucency in a large mediastinal mass which proved to be a lipoma and he felt that the margin of the lipoma was more radiolucent than the rest of the tumor. Seltzer[6] added the observation that the entire tumor, because of its high fat content, may appear less radiopaque than other solid tumors of equal size. These signs were not helpful in the preoperative diagnosis of the four cases presented.

In the differential diagnosis other extrapleural lesions to be considered include metastatic neoplasms. These are actually the most common cause of extrapleural masses and are usually associated with destructive rib changes. Extrapleural hematomas may also present similar radiographic features, but the clinical history of trauma and associated rib fractures will aid in differential diagnosis. Neurogenic tumors and fibromas and mesotheliomas may be indistinguishable radiographically.

Summary

Four cases of extrapleural lipoma are presented and the radiographic characteristics are discussed. Two cases were diagnosed by needle aspiration biopsy and two cases were diagnosed following open thoracotomy.

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LETTERS *to the Editor*

A Caution on Home Deliveries

To the Editor: In the past few years, the practice of giving birth at home has burgeoned in California, having been advocated with considerable eloquence by patients, consumer groups and a gamut of obstetrical attendants. While the fact that delivery at home is often a rewarding experience cannot be argued, expectant parents should also be aware of those potential hazards of childbirth that cannot be properly managed in the home setting, and which can result in unfortunate consequences.

One of the points that is often made by those who offer to supervise home deliveries is that patients are carefully screened to identify those individuals who are unsuitable for this experience because of high risk factors. But the actuality is that many of the complications of labor and delivery cannot be anticipated by even the most skillful of obstetricians. As examples of home delivery gone wrong, I submit the following list of cases that have come to my attention in the past few months, and which I believe represent only a small percentage of the total experience. The patients in all of these cases had to be admitted to hospital after home delivery proved unsatisfactory or impossible.

1. Para 0. One convulsion occurred while patient was in labor at home and two more en route to a hospital, infant born by section was severely depressed.

2. Para 0. Patient was sent to hospital for section after 12 hours in the second stage of labor, infant had clinical evidence of brain damage.

3. Para 3. Patient remained at home for two weeks awaiting labor following spontaneous rupture of membranes, referred to hospital because term infant had died at some point during this interval.

4. Para 0. Membranes ruptured while patient was in labor and during a vaginal examination; she was taken to a hospital in the knee-chest position because of prolapsed cord; the infant was stillborn.

5. Para 0. Patient was sent to hospital after four hours of bearing down at home, infant found to have severe toxemia and an unengaged head. Section required. No blood pressures had been taken.

6. Para 6. Labor induced at home with buccal pitocin, cord prolapsed when membranes ruptured, delivery occurred in a hospital by midforceps of a severely depressed infant.

7. Para 4. Severely depressed breech baby born at home, mother required manual removal of the placenta and transfusion at a hospital, infant had infection that may have been tetanus and the mother had hepatitis.

8. Para 0. Delivery was carried out in a hospital by section after multiple attempts to deliver at home, subsequent severe pelvic infection required hysterectomy and bilateral salpingo-oophorectomy.

9. Five other cases with features similar to the above.

The above recital is not offered as a condemnation of home delivery, but rather to remind those individuals (including some physicians) who tend to regard childbirth as a benign process that disasters can and do occur. While many hospital maternity units can be criticized for their humanistic deficiencies, they can also be congratulated for their ability to handle a wide range of obstetric complications which can threaten life and health.

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Refer to: Michas CA, Wilcox JC, Walters RF: A computer-based surgery reporting system—An entry point to clinical information systems (In the Forefront). West J Med 124: 151-158, Feb 1976

A Computer-Based Surgery Reporting System

An Entry Point to Clinical Information Systems

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In 1973 the University of California, Davis, School of Medicine, purchased outright its principal teaching hospital, the Sacramento Medical Center. The school had previously used the hospital under an affiliation agreement with Sacramento County. With the acquisition and full control of the hospital, opportunities arose for expanded support of the clinical research and teaching activities.

Computer support of clinical activities was all but nonexistent in the Sacramento Medical Center. It was possible, therefore, to investigate new approaches to computer-based information systems that would be responsive to the diverse needs of medical students, house staff and faculty. Interest in computers was generally low among the clinical faculty, owing largely to lack of exposure to useful programs. A favorable element was the availability of a large scale computer serving the Davis campus, eighteen miles from the Medical Center. Another was that a number of basic science research projects on the Davis campus portion of the School of Medicine made use of dedicated (special purpose) minicomputers as well as the central campus system.

Feasibility studies were undertaken in several areas promising substantial returns in the type of information produced and in the cost benefits of the report-preparation process. Because of an early interest in such a system within the Department of Surgery, one such feasibility study was undertaken to provide reports concerning all patients admitted to or operated upon by the general surgery services.

In this report we describe the types of data collected, the methods used for data input and the reports generated as a result of this pilot study. Its cost-effectiveness is studied, and the potential for increased utilization of the clinical information is discussed. Finally, the potential for incorporation of this project into a coordinated clinical information system is analyzed.

Objectives of Study

The team that undertook this pilot study was interested in accomplishing several separate objectives. The chief objectives identified in the project were:

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ABBREVIATIONS USED IN TEXT

H-ICDA = *Hospital—International Classification of Diseases, Adapted*

MC/ST = Magnetic Card Selectric Typewriter (IBM)

- Investigation of clinical research applications available through computerization of data;
- Development of a more efficient method for generating house staff, department and hospital statistical reports;
- Exploration of new data entry methods for creation of machine-readable information;
- Development of increased awareness among clinical faculty of potential for computer assistance in using clinical data.

The investigators hoped, in addition, to provide sufficient visibility through this project to generate interest in expanded clinical support systems. Since the project was a pilot study developed without formal support from either intramural or extramural sources, it was necessary to carry out the investigation within the confines of available computer and secretarial support and with a minimum of disruption of existing activities. There were no funds available to produce new input forms or keypunch data, or to provide for professional programming. The investigators therefore undertook this study as a spare time activity in addition to their regular obligations, recognizing the possibility for long-term benefits if the project proved successful. Some departmental funds were secured for the machine time costs incurred in data processing and program debugging. No other direct costs were incurred during the feasibility study.

Description of Data Base and Reporting Requirements

The need for a growing number of reports relating to patients treated by the Department of Surgery has created increasingly burdensome clerical load requiring the frequent repetition of similar information in different reporting formats. Among the groups requiring information on patient encounters are Medical and Surgical Specialty Boards, Professional Standards Review Organizations (PSRO) agencies, third party payers, the Association of American Medical Colleges (AAMC) and the Joint Commission on Accreditation of Hospitals (JCAH). To this list should be added internal reports useful to departments, administration and individual researchers.

Analysis of the type of information required by these various groups led to development of a manual report form which included several types of data:

- Patient identification (name, year of birth, sex, unit number, ward or "private" patient);
- Admission and discharge dates, discharge diagnoses, external trauma code;
- Operation (procedures)—operation code, major or minor, type of anesthesia, date and shift, elective or emergency, surgeons (including level of responsibility);
- Complications, death and autopsy information.

Figure 1 indicates the format in which these data are recorded on the resident's reporting form. Numeric or alphabetic codes are used to identify several elements within this record. *Hospital International Classification of Diseases, Adapted* (H-ICDA) codes are numeric and indicate diagnoses and procedures. Numeric codes assigned by the hospital identify participating surgeons. Other codes are self-explanatory as noted in Figure 1.

Responsibility for completion of the basic information rests wth the chief resident of each of the surgical services who enters these data manually each day into the Ward Service Book. At the end of each month, the H-ICDA codes are entered by a trained record librarian for the diagnoses, external trauma and operative procedures. This restriction of reporting responsibility reduces the potential for inconsistencies in reporting procedures.

In the conventional manual reporting processes, some of the data available on the Ward Service Reports were then typed into a variety of separate reports at monthly or less frequent intervals. Because of the differing formats of the various required reports, the amount of repetitive typing generated by this process usually led to excessive clerical activity each month.

Computerization of Data

As noted previously, no trained keypunch operators were available, nor were there any facilities for card entry under remote job systems. However, the project members had independently developed techniques for computer entry of data typed onto magnetic cards used by the IBM Magnetic Card Selectric Typewriter (MC/ST). It was decided that this method of data transcription would be used for two reasons: (1) because the equipment was available and (2) because the

DEPARTMENT _____ UNIVERSITY OF CALIFORNIA, DAVIS – DIVISION OF SURGICAL SERVICES SERVICE _____ MONTH _____ YEAR _____

NO	NAME	UNIT NUMBER		DISCHARGE DIAGNOSES	CODE	E CODE	DISCH (Transf) DATE	OPERATION (PROCEDURE)	CODE	MAJ MIN	OPER DATE	EL EM	SURGEONS	C O O E	W P	Death Time
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RESIDENT STAFF REPORT DATE:JULY 1999 SERVICE:BLUE SERVICE PAGE NO. I

	NAME	RANK	CODE	TOTAL	PERSONAL	SERVICE	SURG	ASST	MAJOR	MINOR	ELECT	EMERG	E-CODE	NO	E-CODE	O/C	NO O/C
869	GORDON, CHARLES H.	R4	5260	8	0	8	6	2	8	0	5	3	2		6	0	8
930	SHAPRIO, PETER D.	R3	5269	5	0	5	5	0	4	1	1	4	0		5	0	5
1013	OIVITTORIO, ALBERT	R1	5258	3	0	3	0	3	3	0	2	1	0		3	0	3
1090	MILLER, ROBERT G.	IR	5001	1	0	1	0	1	1	0	0	1	0		1	0	1
1107	DEVEREAUX, DENNIS F	S1	5031	4	0	4	0	4	4	0	3	1	2		2	0	4

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ATTENDING STAFF REPORT DATE:JULY 1999 SERVICE:BLUE SERVICE PAGE NO. I

	NAME	RANK	CODE	TOTAL	PERSONAL	SERVICE	SURG	ASST	MAJOR	MINOR	ELECT	EMERG	E-CODE	NO	E-CODE	O/C	NO O/C
30	BABBIN, GEORGE	AS	0120	1	0	1	0	1	1	0	1	0	1		0	0	1
259	GARFINKLE, SID E.	AS	0931	1	0	1	0	1	1	0	0	1	0		1	0	1
518	MICHAS, CONSTANTINE	AS	0775	4	0	4	0	4	4	0	3	1	0		4	0	4
826	WOLFMAN, EARL F JR.	AS	0613	1	0	1	0	1	1	0	1	0	0		1	0	1

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EXTERNAL INJURY REPORT DATE:JULY 1999 SERVICE:BLUE SERVICE PAGE NO. I

	NAME	UNIT #	DIAGNOSIS CODES	CODE	EXTERNAL INJURY	ADMT DSCH	PROC DATE SURG
B I	ROBERTS,HOBB	991230	F51 947.2	E924	ACC BY HOT SUBST CORROSIVE LIQ STEAM	0701 0702	
B I	MARTINEZ,JOS	537912	M18 785.2 242.2 820.4	E929	OTHER AND UNSPECIFIED ACCIDENTS	0626T0816	43.0 0708 5260
B I	WILMER,WILMA	892367	F32 864.1 852.0	E929	OTHER AND UNSPECIFIED ACCIDENTS.	0717 0724	42.0 0717 5260
B I	THOMAS,DIANE	422521	F12 998.5	E947	LATE EFFECT OF SURGICAL OPERATION	0701 0703	
B I	JACKSON,JOHN	226722	M36 560.9 990.6 009.2	E948	LATE EFFECT OF IRRADIATION	0701 0714	
B I	WILLIAMS,LEN	032441	M77 879.9 682.4	F969	LATE EFFECT INJ INFL BY OTHER PERS	0705 0708	

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DIAGNOSIS REPORT DATE:JULY 1999 SERVICE:BLUE SERVICE PAGE NO. 1

	NAME	UNIT #	DIAGNOSIS CODES	CODE	DIAGNOSIS	ADMT DSCH	PROC DATE SURG
B I	CAMERON,BRUC	212344	M22 009.2	009.2	DIARRHEAL DISEASE	0701T0704T	39.1 0701 5269
B I	SCHOLTZER,A	212432	M58 009.2 569.4	009.2	DIARRHEAL DISEASE		47.5 0710 5260
B I	JACKSON,JOHN	226722	M36 560.9 990.6 009.2	009.2	DIARRHEAL DISEASE	0701 0714	
B I	ABRAMSON,LIN	91253	F89 150.0 196.9	150.0	MALIGNANT NEOPLASM OF ESOPHAGUS	0709 0713	A1.6 0710 5260
B I	ABRAMSON,LIN	91253	F89 150.0 196.9	196.9	SEC AND UNSPEC MAL NEO OF L NODES	0709 0713	A1.6 0710 5260
B I	MARTINEZ,JOS	537912	M18 785.2 242.2 820.4	242.2	THYROTOXICOSIS WITH OR WITHOUT GOITER	0626T0816	43.0 0708 5260
B I	FARMER,ADAM	771231	M52 445.9 250.9	250.9	DIABETES MELLITUS	0713T0726	
B I	AARON,ANNA	876123	F03 707.0 349.3	349.3	OTHER DISEASES OF SPINAL CORD		A7.8 0703 5269
B I	FARMER,ADAM	771231	M52 445.9 250.9	445.9	GANGRENE	0713T0726	
B I	CLARK,KENT	020304	M38 533.0	533.0	PEPTIC ULCER SITE UNSPECIFIED	0708T0717	A8.4 0708 5269
B I	ROMERO,JESSE	558221	M02 540.9	540.9	ACUTE APPENDICITIS	0723 0725	41.1 0723 5269
B I	HOMMELL,AMY	054301	F92 550.0	550.0	ING HERNIA WITHOUT MENTION OF OBS	0723 0725	38.2 0724 5260
B I	JACKSON,JOHN	226722	M36 560.9 990.6 009.2	560.9	INTES OBST WITHOUT MENTION OF HERNIA	0701 0714	
B I	SCHOLTZER,A	212432	M58 009.2 569.4	569.4	OTHER DIS OF INTESTINE AND PERITONEUM		47.5 0710 5260
B I	LITTLESON,MO	221889	F66 574.0	574.0	CHOLELITHIASIS	0702 0707	A3.5 0703 5260
B I	GEORGE,TOM	324678	H59 682.4	682.4	OTHER CELLULITIS AND ABSCESS	0722 0725	
B I	HSU,LIN	123426	F16 682.4	682.4	OTHER CELLULITIS AND ABSCESS	0722 0725	A4.4 0722 5269
B I	WILLIAMS,LEN	032441	M77 879.9 682.4	682.4	OTHER CELLULITIS AND ABSCESS	0705 0708	
B I	AARON,ANNA	876123	F03 707.0 349.3	707.0	CHRONIC ULCER OF SKIN		47.8 0703 5269
B I	MARTINEZ,JOS	537912	M18 785.2 242.2 820.4	785.2	SYMP REF TO ABD AND LOWER GI TRACT	0626T0816	43.0 0708 5260
B I	RIGGINS,ROBT	338922	M37 785.5	785.5	SYMP REF TO ABD AND LOWER GI TRACT	0723 0724	
B I	MARTINEZ,JOS	537912	M18 785.2 242.2 820.4	820.4	FRACTURE OF UPPER END OF FEMUR	0626T0816	43.0 0708 5260
B I	WILMER,WILMA	892367	F32 864.1 852.0	852.0	SUBARACH SUBD , EXTRAD REM INJURY	0717 0724	42.0 0717 5260
B I	WILMER,WILMA	892367	F32 864.1 852.0	864.1	INJURY TO LIVER	0717 0724	42.0 0717 5260
B I	WILLIAMS,LEN	032441	M77 879.9 682.4	879.9	OTHER MULT , UNSPEC OPEN WOUNDS OF UN.T	0705 0708	
B I	ROBERTS,HOBB	991230	F51 947.2	947.2	BURN INVOLVING TRUNK WITH LIMBS	0701 0702	
B I	JACKSON,JOHN	226722	M36 560.9 990.6 009.2	990.6	EFFECTS OF RADIATION	0701 0714	
B I	THOMAS,DIANE	422521	F12 998.5	998.5	OTHER COMPLICATIONS OF SURG PROC	0701 0703	

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OPERATION REPORT DATE:JULY 1999 SERVICE:BLUE SERVICE PAGE NO. I

	NAME	UNIT #	DIAGN	ADMT DSCH	PROCEDURE CODES	CODE	PROCEDURE	DATE	SURG
B I	HOMMELL,AMY	054301	F92 550.0	0723 0725	38.2 92.0	38.2	REPAIR ING HERNIA EXCEPT RECURRENT	GMAJ0724ELI	5260
B I	CAMERON,BRUC	212344	M22 009.2	0701T0704T	39.1	39.1	EXPLORATORY LAPAROTOMY OR CELIOTOMY	GMAJ0701EM2	5269
B I	ROMERO,JESSE	558221	M02 540.9	0723 0725	41.1	41.1	APPENDECTOMY	GMAJ0723EM3	5269
B I	WILMER,WILMA	892367	F32 864.1 E929	0717 0724	A2.0	42.0	HEPATOTOMY	GMAJ0717EM3	5260
B I	MARTINEZ,JOS	537912	M18 785.2 E929	0626T0816	A3.0	43.0	INCISION OF BILE DUCTS	GMAJ0708EL1	5260
B I	LITTLESON,MO	221869	F66 574.0	0702 0707	43.5	A3.5	CHOLECYSTECTOMY	GMAJ0703ELI	5260
B I	SCHOLTZER,A	212432	M58 009.2		A7.5 47.4	47.A	RESECTION OF SMALL INTESTINE	GMAJ0710EM2	5260
B I	SCHOLTZER,A	212432	M58 009.2		47.5 A7.4	47.5	RESECTION COLON,PARTIAL OR #SUBTOTAL	GMAJ0710EM2	5260
B I	AARON,ANNA	876123	F03 707.0		47.8	47.8	COLOSTOMY	GMAJ0703EL1	5269
B I	CLARK,KENT	020304	M38 533.0	0708T0717	A8.4	A8.A	ENTEHORRHAPHY	GMAJ0708EM1	5269
B I	HOMMELL,AMY	054301	F92 550.0	0723 0725	38.2 92.0	92.0	INC SKIN AND SUBCUTANEOUS TISSUE	GMAJ0724ELI	5260
B I	ABRAMSON,LIN	91253	F89 150.0	0709 0713	A1.6 A1.9	A1.6	BIOPSY OF THORAX	GMAJ0710EL1	5260
B I	ABRAMSON,LIN	91253	F89 150.0	0709 0713	A1.6 A1.9	A1.9	BIOPSY BIL TRACT,SPLEEN AND PANCREAS	GMAJ0710EL1	5260
B I	HSU,LIN	123426	F16 682.4	0722 0725	A4.4	A4.4	ESOPHA AND GASTROSCOPY S EFFECT LES	NMIN0722EM2	5269

Figure 2.—Samples of reports produced from input data (names of patients are fictitious).

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STATISTICS REPORT ON OPERATIONS DATE:JULY 1999 SERVICE:COMBINED SERVICES PAGE NO. 1

	BLUE	GOLD	WHITE	TOTAL
WARD	11	2	7	20
PERSONAL	0	0	1	1
TOTAL	11	2	8	21
E CODE	2	0	2	4
NO E CODE	9	2	6	17
MALE	5	2	3	10
FEMALE	6	0	5	11
0-2	0	0	0	0
3-15	1	0	1	2
16-30	1	0	0	1
31-40	1	1	0	2
41-50	1	0	2	3
51-60	3	1	2	6
61-70	0	0	2	2
71-80	2	0	1	3
81-90	2	0	0	2
91+	0	0	0	0

	BLUE	GOLD	WHITE	TOTAL
ANESTHESIA				
NONE	1	0	0	1
LOCAL	0	1	3	4
REGIONAL	0	0	0	0
GENERAL	10	1	5	16
SHIFT				
7-3	6	1	6	13
3-11	3	1	2	6
11-7	2	0	0	2
OUTPATIENT	0	0	0	0
INPATIENT	11	2	8	21
ON SERVICE	7	2	5	14
NOT ON SERVICE	4	0	3	7
MAJOR	10	1	6	17
MINOR	1	1	2	4
ELECTIVE	5	2	4	11
EMERGENT	6	0	4	10

Figure 2. (con't)—Samples of reports produced from input data (names of patients are fictitious).

secretaries in the Department of Surgery were familiar with these machines and hence data entry would represent a minimum departure from previous manual methods.

Accordingly, a method was devised for consistent entry of the data from Ward Service Books onto MC/ST cards. Secretaries in the department prepared the cards, and the data were then entered into the computer via a remote terminal consisting of an MC/ST equipped with communications capability. A special program was written to accept the data thus transmitted; a second program screened the initial input data, reporting on inconsistencies or missing data. The resulting printout was returned to the departmental secretary who, together with the chief resident, resolved these discrepancies and corrected the input file through interactive terminals. The final file was then available for processing through the report generator program.

Reports Produced by Pilot Study

Although the data available for each patient appear in one sequence on a single line of the Ward Service Book (Figure 1), they could be arranged to produce a variety of different reports in the desired format as noted below. Samples of some of the reports created for this study are included as Figure 2.

Table 1 summarizes the type of information reported in monthly and annual reports for each service and for the combined services. As indicated by the various codes in that table, in each report some items are omitted to permit expansion of other data elements. Some information is reproduced in coded form, whereas other items are interpreted and spelled out in English terms or names. Each report is sorted according to the information most pertinent for that summary.

In order to create written English word equivalents of the various codes in the original input data, it is necessary to have the following separate dictionaries in the computer:

- An operative procedure dictionary (H-ICDA terminology): approximately 1,000 procedures, each represented by up to 48 characters of English terminology;
- A diagnosis dictionary (H-ICDA code, decimal portion omitted): approximately 1,000 codes, each represented by up to 48 characters of English terminology;
- An external source of injury dictionary (H-ICDA terminology, decimal portion omitted): approximately 200 entries, each represented by up to 48 characters of English terminology;
- A physician code dictionary: approximately 1,100 house officers and attending physicians, contains physician's last name, first name, rank and number code as assigned by the hospital (revised annually);
- Equivalence dictionary: a series of equivalences between H-ICDA operation codes and operative groupings required by American Board of Surgeons Residency Record.

In addition, several other codes with only a few alternatives are interpreted and spelled out in certain reports. Implicit groupings such as age distributions are calculated from appropriate input parameters.

TABLE 1.—*Types of Information Reported in Monthly and Annual Reports for Each Service and for the Combined Services.*

	Total Number Operations	Level of Participation	Major/Minor	Elective/ Emergency	External Trauma	Death/ Complications	Post-Operation Time of Death	Autopsy	Patient's Name	Patient's I.D. Number	Patient's Year of Birth	Patient's Sex	Ward/Private	Inpatient or (which service) Outpatient	Date Admitted	Date Discharged	Date of Operation	Shift when Operation Began	Operative Procedure Codes	Diagnosis Codes	Type of Anesthesia	Surgeon's Code Numbers
A. Monthly Individual Service Reports																						
1. For each house officer	x	x	x	x	x	x	--	--	--	--	--	--	x	--	--	--	--	--	--	--	--	--
2. For each attending staff	x	x	x	x	x	x	--	--	--	--	--	--	x									
3. Operations summary (sorted by operation code)	--	--	v	v	c	c	c	--	v	v	v	v	v	c	d	d	d	c	p	c	v	c
4. Diagnosis summary (sorted by diagnosis)	--	--	--	--	--	c	c	--	v	v	v	v	--	c	d	d	d	--	c	p	--	c
5. External injury summary (only where external source of trauma reported)	--	--	--	--	p	c	c	--	v	v	v	v	--	c	d	d	d	--	c	c	--	c
6. Complications summary	--	--	--	--	--	p	--	--	v	v	v	v	--	--	d	d	d		c	--	--	c
7. Mortality summary						p	c	c	v	v	v	v	--						c			c
B. Monthly Combined Service Reports (1-7: same format as A above)																						
8. Admissions summary	--	--	--	--	t	--	--	--	--	--	t	t	t	t	--	--	--	--	--	--	--	--
9. Operations summary	t	--	t	t	t	--	--	--	--	--	t	t	t	t	--	--		--	--	--	t	--
10. Overall experience	t	--	--	--	t	t	t	s	--	--	t	t	--	t	--	--		--	--	--	--	--
C. Annual Reports (1-10: see B above)																						
11. American Board of Surgery resident report																						

x = Total number in category
v = Information present in report
-- = Information absent in report
c = Codes listed in report
p = Primary code interpreted
d = Dates
t = Summary Tables (by service, age group, etc.)
s = Tables with percentages

Cost Analysis

The subject was not undertaken in a manner that would permit rigorous comparison of actual development costs with similar manual techniques. As noted above, the project team members devoted significant portions of their free time to this project in order to achieve their goals. Approximately $200 was provided for machine time during the development phase, and a portion of one secretary's time was also used in data entry over and above the parallel manual process.

If, however, one considers operational costs of the developed package alone, the recurrent expenses are as shown in Table 2. To this comparison should be added the facts that (1) accuracy of reporting has increased through the computer input method; (2) reports are available more rapidly than through manual methods, and at greater frequency; (3) for annual reports, work load is distributed throughout the year rather than concentrated at year-end, and (4) some valuable reports previously unavailable are produced through the new method.

Discussion

The entry of approximately 20 items of information about each patient managed by the General Surgery services permits preparation of a wide variety of different reports, each emphasizing different data elements, sorted in appropriate sequences and put ino a format to stress the pertinent data. The merits of such a reporting system will be obvious to anyone who has attempted to generate similar data from manual records. Because the value of the system was carefully worked out and explained, and since the project required relatively little additional effort on the part of the participating department, it was well accepted during the feasibility study period. Despite initial skepticism on the part of the participating department, the reports have proven sufficiently valuable that they have received generally enthusiastic department support once a total year's results could be shown. The summary reports generated at the end of the first year persuaded the department to provide formal financial support for its continuation.

Several unexpected benefits were observed by department members. The errors that were detected were initially assumed to be the function of computerizing the data. It was soon discovered, however, that the bulk of these errors appeared in the residents' original reports. Timely feedback

TABLE 2.—*Summary of Recurrent Expenses for Operational Costs of the Developed Package Alone.*

	Costs of Computer System
1. Data preparation by resident	Constant*
2. Initial typing of data on MC/ST (8 hrs/mo)	$ 32
3. Data entry to computer, initial checkout (mo)	10
4. Error detection, recovery (2 hrs/mo)	8
5. Preparation of monthly reports	5
6. Preparation of annual reports	60
Total annual cost	720

*Constant for both methods.

methods described in the input procedure section soon led to increased accuracy in the residents' reports. Preparation of diagnosis and operative summary reports provided, at a glance, valuable information regarding the total experience within different categories. Length of stay and other data that are becoming increasingly important in utilization reviews and medical care audits became immediately available from these summaries. These findings were of particular value since the current administrative hospital information system was unable to produce similar statistics from their records.

Because the data are in machine readable form, it is possible to consider research investigation of many other relationships. While the full potential of this capability remains to be explored, the department has already begun to awaken to some of these possibilities, and to accept the computerized system with increasing enthusiasm.

The long-range implications of this feasibility study, therefore, are several. In addition to providing a cost-effective method for preparing reports currently required or desired by internal or external groups, the methodology resulted in improved records and opened the door to a more rigorous examination of clinical factors previously not available for analysis. Equally important, the study raised the acceptability of computer-based information systems in a clinical setting. This factor is important considering the ultimate potential of an integrated information system aimed at clinical research, teaching and patient care. Coupled with other studies of a similar nature, these early results may well pave the way for educated participation of clinical staff in planning for such information systems. Without such participation, the success of any computer project in a clinical setting is open to serious question.

Future Areas of Investigation

The study showed that data entry techniques may provide cost-effective ways for improving information available to a clinical department. However, several design elements inherent in the nature of this study limited its efficiency. Resolution of some of these limitations would significantly improve the overall success of future studies of this type.

Because computerized patient identification and basic admission data were not available from hospital administrative sources, it was necessary to enter a considerable body of data that is not specific to the surgery service for which the study was undertaken. Creation of pooled patient identification records in machine readable form and readily available to clinical investigators would greatly facilitate the further development of such projects. If these data were on-line, they would vastly increase the ability of such a project to provide reports in a timely manner.

The input technique (use of MC/ST) cards proved successful in the data preparation phase, but transmission through timeshare terminal is an unnecessarily long process requiring clerical monitoring of the terminal while data already in machine readable form are sent at low rates over telephone lines. This technique can be significantly improved if high speed magnetic card transports are interfaced directly to a computer (even a minicomputer), making the data immediately available for further processing. Such a transport does exist and is being installed for use at the Sacramento Medical Center at the time of this writing.

Availability of other data bases pertinent to the patients treated in this service would greatly add to the research relevance of the system. Such information as might be generated through examination of biopsy specimens, autopsy material or laboratory data would seem to be particularly appropriate to merge with the information recorded in this study. Such data combination can be accomplished even without a complete hospital information system if a coordinated plan exists for gathering such data and for sharing the results between different concerned groups.

A further dimension of this program is that there exists potential participation by many teaching centers, thereby making readily available a huge volume of information that can be

the basis of clinical studies to evaluate management of diseases for which inadequate data to base solid conclusions on exist in any one of these centers. With such an extended program, large cooperative studies could be carried out to answer such questions as which is the most effective method of treating carcinoma of the breast.

Summary and Conclusions

The study described above was undertaken to develop an efficient method for providing a wide variety of reports on patient treatment within a single department in a hospital otherwise unaffected by clinical support systems. Its success in achieving these basic objectives also led to a pronounced increase in the acceptance of the computer as a clinical tool, thus opening the door for future studies that could provide a more integrated hospital information support system. Several specific improvements in data collection and coordination are suggested. The authors feel that carefully planned computer support projects can in fact lead to better use of clinical information in direct patient care as well as provide the data base for clinical investigations and required statistical reports.

Falsely-High Cholesterol Levels When the Tourniquet Is Left on the Arm Too Long

Now, I'll tell you something about a cholesterol measurement that I'll bet most of you don't know, and that is every five minutes you leave a tourniquet on, the blood cholesterol level rises 10 mg . . . I'm not saying that you can't find the vein, but a nurse or technician who maybe has not done very many of these tests might not be able to find the vein very quickly and so they keep the tourniquet on, keep poking away. Now, look what happens: hemo-concentration occurs as a result of this. The water is squeezed out and so the cholesterol level rises. So now instead of having a blood cholesterol level within a normal limit (in Cleveland, 233 is the average), this may rise to around 260 by the time you get it. Now you see you have converted the patient. You're going to have to tell him "Look, you're in trouble because you've got high blood cholesterol" and that scares the devil out of him. It may not be true; it may be true. But I'm simply trying to point out that one little practical aspect is to be able to take the blood cholesterol level and get a correct answer before you condemn a person to changing his whole way of life. Now, that's putting a lot of emphasis on one or two measurements of blood cholesterol.

—IRVINE H. PAGE, MD, *Cleveland*
Extracted from *Audio-Digest Family Practice,* Vol. 23, No. 44, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Boulevard, Suite 700, Los Angeles, CA 90057.

Refer to: Mahoney LE: Air pollution and respiratory mortality in Los Angeles (Environmental Health). West J Med 124:159-166, Feb 1976

Air Pollution and Respiratory Mortality in Los Angeles

LOUIS E. MAHONEY, MD, Dr PH, *San Bernardino*

An epidemiologic study in Los Angeles showed a regular statistical association between respiratory mortality and the spatial distributions of ozone and particulate matter. There was an irregular association of respiratory mortality with maximum temperature. These findings are consistent with those of other studies relating respiratory morbidity to oxidant and particulate air pollution, and suggest that these pollutants may be health hazards.

AIR POLLUTION in Los Angeles has caused considerable political and technical concern for a generation. Despite 25 years of research, however, no consistent studies have appeared to describe the effects of the city's oxidant air pollution on human health. Mills[1,2] suggested a significant influence of oxidant air pollution on daily mortality from cardiac and respiratory causes; results in studies by a group from the California State Health Department[3-5] do not confirm this finding. Sterling and others[6-8] have reported that increases in hospital admissions for a number of diseases were related to daily concentrations of oxidants and other pollutants.

Findings in a preliminary study of respiratory mortality in Los Angeles[9] showed that death rates from respiratory disease were increased in downwind areas of the city. The increase was independent of different age, sex and income characteristics of different "wind zones" within the city. These findings were consistent with an effect of air pollution or of some meteorologic factor associated with wind flow.

Sources of air pollution in Los Angeles are predominantly diffuse. The troublesome primary pollutants of other areas—principally sulfur oxides and particulates—are less prominent in Los Angeles because of economic and climatic differences. Oxidant, however, accumulates within masses of air as they move across the city. This secondary pollutant could be responsible for the mortality increase associated with wind flow.

In order to shed more light on respiratory disease in Los Angeles, it seemed reasonable to examine mortality for association with each of the "classical" air pollutants known to be associated with respiratory disease elsewhere, and for association with oxidant. The principal climatologic covariates of oxidant—maximum and minimum temperature—were examined at the same time. A spatial model was tested, rather than the temporal models studied by other investigations.

From the School of Public Health, University of California, Los Angeles, and the Los Angeles County Health Services Department.

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Reprint requests to: Louis E. Mahoney, MD, Dr PH, Director of Public Health, County of San Bernardino, 351 N. Mountain View Avenue, San Bernardino, CA 92415.

ABBREVIATIONS USED IN TEXT
DMHA = daily maximum hourly averages
IDM = instantaneous daily maximum

Methods

Statistical considerations mandated a study period closely related to a decennial census. The study was begun in 1968, when data from the 1969-1971 pericensal period were not yet available. Inconsistencies in tabulation of 1959-1960 and 1961 data prevented merger of these years. The 1961 data set was chosen therefore in order to use the more detailed geographical divisions of the 1960 census. Lack of funding has prevented repetition of the study with 1969-1971 data.

Methods of investigation were essentially the same as those of the wind flow study.[9] Charts of the spatial distribution of suspected pollutant or meteorologic variables were used to assign a representative level of exposure for each variable to all census tracts of the city. The populations of these tracts were then pooled by levels of each variable under consideration, and mortality rates were computed for each level, adjusted for different age, sex and income characteristics of the different groups. A chi-square statistic was used to test the hypothesis that there was no difference in mortality between levels of exposure.

Pollutant data. The Los Angeles County Air Pollution Control District provided charts of isopleths of 90th percentile daily maximum values of ozone, sulfur dioxide and suspended particulates for the year 1961. These charts were enlarged onto standard census tract maps using a pantograph, with an estimated mechanical accuracy of half a mile. Six to nine pollutant stations were used to estimate pollution distributions; two stations 13 miles apart provide the only data for the San Fernando Valley, while up to eight stations generally about 5 miles apart provide data for the remainder of the city. This potential source of error is partly counterbalanced by the larger area and lower population density of census tracts in the San Fernando Valley, which tend to minimize the effect of malpositioning of boundaries between pollutant levels.

Temperature data. Temperature data were obtained from routine publications of the Weather Bureau[10] in the form of charts of isotherms of January mean minimum temperature and July mean maximum temperatures for the years 1931-1952. These charts were reproduced photographically and projected on census tract maps by a camera-lucida arrangement, with an estimated error in position of a quarter mile. These charts represent 21 year means from 18 data collecting stations generally less than five miles apart. The precision of estimates is somewhat lower in mountainous areas than on the plain, but this is of slight effect because the mountainous areas are very sparsely populated. These data need not specifically refer to the year 1961, as the spatial distribution of maximum and minimum temperatures does not change radically from year to year.

Data processing. The census tract maps thus obtained for pollutant and temperature variables were examined, and each tract was assigned the value shown by the immediately lower isopleth or isotherm. Intermediate values were not interpolated. Between isopleths representing 20 and 22.5 parts per 100 million (pphm) of ozone, for instance, all tracts would be assigned the value 20. These values were keypunched in sets for each variable and screened on the computer for duplicate or missing values, and a sample was then manually rechecked for accuracy. They were then copied onto online disk storage along with 1960 census data by tract to facilitate further processing.

Census and death data utilized were identical to those used in the pilot study,[9] except that all census tracts of the city were available for analysis. The white population of the city at the time of the 1960 census was again taken as the study population. Death certificates from the year 1961 were obtained on magnetic tape, and sorted for respiratory deaths due to causes coded 241, 470-

TABLE 1.—*Selected Respiratory Deaths by Cause, Los Angeles White Study Population, 1961*

ICD Code*	*Cause of Death*	*Deaths*
241	Asthma	61
470-475	Upper respiratory infections	9
480-483	Influenza	29
490-493	Pneumonia	597
500-502	Bronchitis	49
510-517	Other upper respiratory diseases	8
518-521	Pleurisy, empyema, pneumothorax, and lung abscess	14
525	Other nonoccupational interstitial pneumonias	48
526	Bronchiectasis	33
527	Other diseases of lung and pleura	198
	All selected deaths	1,046

*International Classification of Diseases, 7th Revision, 1957

TABLE 2.—*Respiratory Mortality by Age and Sex, Los Angeles City White Residents, 1961*

Age	Male		Female	
	Population	Rate/100M	Population	Rate/100M
0-4	98,226	74.3	94,983	57.9
5-14	170,403	3.5	165,385	3.0
15-24	113,813	1.8	125,100	2.4
25-34	137,967	4.3	135,762	2.9
35-44	149,653	13.4	156,873	4.5
45-54	128,408	28.8	136,412	16.9
55-59	54,115	64.7	60,253	36.5
60-64	44,951	140.2	54,869	45.6
65-69	37,636	225.8	49,360	46.6
70-74	28,120	380.5	39,276	109.5
75+	29,265	734.7	49,746	375.9

TABLE 3.—*Standardized Mortality Ratios (SMR) and Mortality Rates for Respiratory Diseases by Level of Income, Adjusted for Age and Sex, Los Angeles City Whites, 1961*

Income Level*	Population	Deaths		Mortality	
		Expected	Actual	SMR	Rate/100M
$8,430+	517,870	202	145	72	36.4
$7,350-8,429	482,414	198	151	76	38.7
$6,228-7,349	471,134	248	224	90	45.8
$5,153-6,227	362,862	230	244	106	54.0
$ 0-5,152	226,296	168	282	168	85.2

$\chi^2 = 108.0$, 4df, $P << 0.001$

*Median family income of tract of residence, 1960 census.

521 and 525-527.9 in the International Classification of Diseases. The distribution of specific causes of death is shown in Table 1.

Deaths and census data were read in by processing programs by census tract. The pollutant or temperature value for each tract was ascertained, and tracts were then pooled in internal matrices of age, sex, income level and up to five levels of the particular pollutant or temperature variable. Conventional mortality statistics were computed, including age-, sex- and income-specific mortality rates. These rates were used as standards to compute rates for each level of the particular pollutant or meteorologic variable, adjusted by the indirect method for age, sex and income level. For each computation a chi-square statistic was calculated as: $\chi^2 = \sum_{i=1}^{n} \frac{(Do_i - De_i)^2}{De_i}$ where Do_i = actual deaths in the ith pollutant level; De_i = expected deaths in the ith pollutant level on the basis of its age, sex and income composition; n = number of pollution levels.

This statistic was used to test the hypothesis that there is no systematic difference in mortality according to pollutant levels. Two observations were felt necessary for rejection of this hypothesis: first, that a chi-square statistic be obtained that would not occur more than 5 percent of the time by chance, if there were no true difference by pollutant level; second, that there must be a systemic increase in mortality parallel to change in the suspected independent variable. The first of these criteria is perhaps overly sensitive and not very specific, as any number of extraneous variables may contribute to apparent differences between groups. The second criterion is rather insensitive, as it is possible that confounding variables might have ordered spatial distributions different from that of the particular variable under consideration, and obscure its effect. Both of these situations are reflected in the study findings.

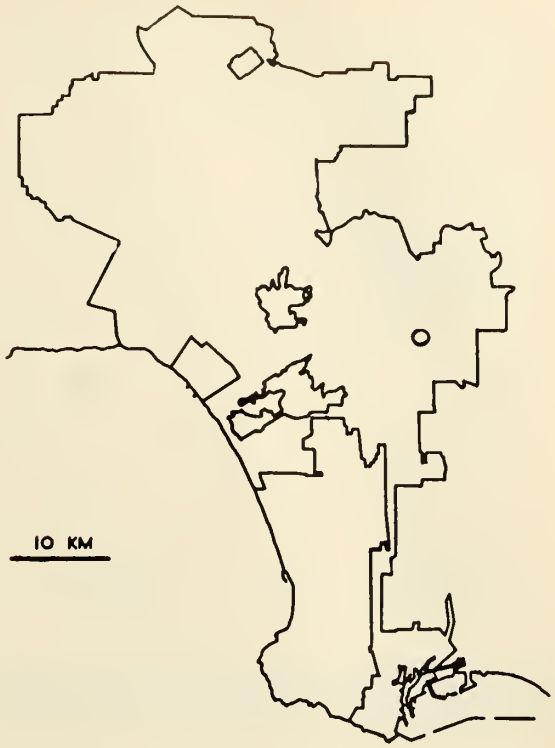

Figure 1.—Los Angeles city limits in 1960, for orientation of Figures 2-6. Circle shows position of Civic Center.

The standard rates used for internal adjustment differ from those used in the pilot study, since they represent the entire city. In all, 1,046 deaths due to the selected respiratory causes were available for analysis. The distribution of these causes does not differ greatly from the distribution of causes used in the pilot study. The crude mortality rate in the entire city was 50.8 per 100,000. Age- and sex-specific rates for the entire white popula-

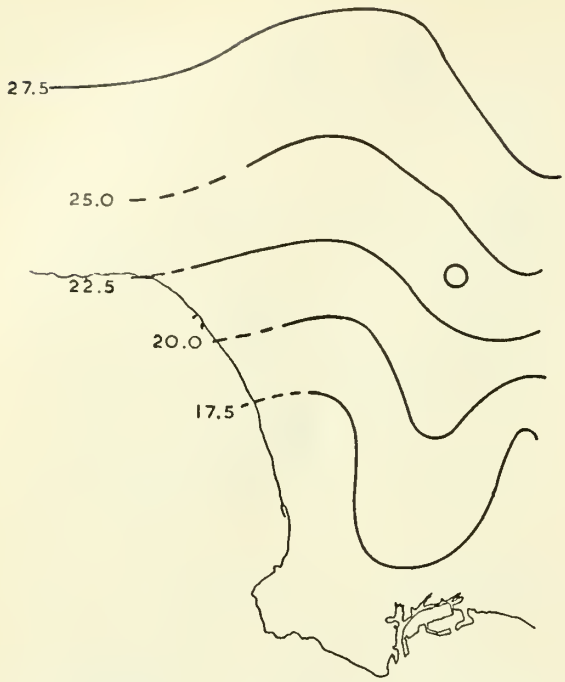

Figure 2.—Isopleths of 90th percentile instantaneous daily maximum of ozone (by neutral KI), pphm, 1961. Circle shows position of Civic Center.

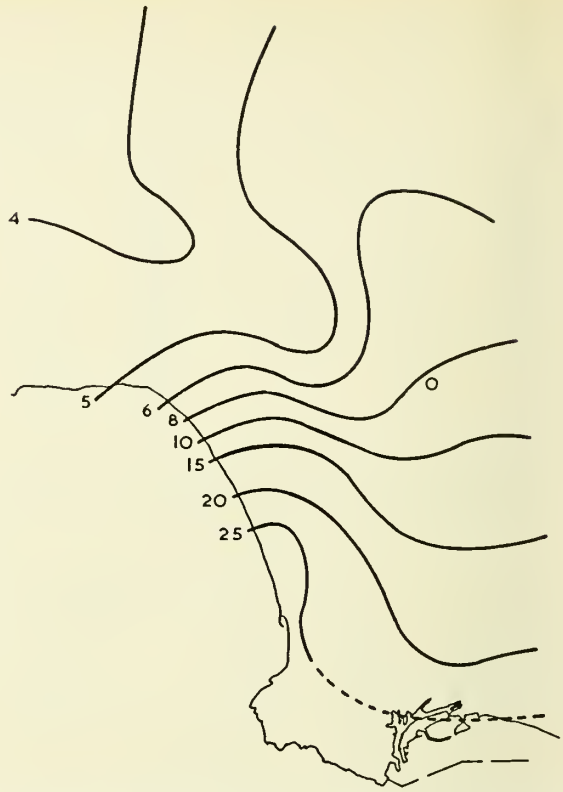

Figure 3.—Isopleths of 90th percentile instantaneous daily maximum of sulfur dioxide, pphm, 1961. Circle shows position of Civic Center.

tion are shown in Table 2. Adjusted mortality rates by level of income are shown in Table 3. These rates vary slightly from those previously observed in the pilot study areas.

Results

Oxidant. First, the distribution of oxidant was examined. A chart of isopleths of 90th percentile instantaneous daily maximum (IDM) of "ozone" (by the neutral KI method) is shown as Figure 2. (Figure 1 shows Los Angeles city limits in 1960 for orientation of Figures 2 through 6.) Although the measurements are very closely correlated,[11] other oxidants than ozone are measured by the potassium iodide (KI) method. In this study, therefore, "ozone" is considered as equivalent to earlier measurements of "total oxidant" measured by the neutral KI method. Note in Figure 2 that levels of ozone or oxidant increase from the shore inland, resembling the previously studied wind model rotated to the left.

Mortality rates for respiratory disease by ozone level are shown in Table 4. There is a systematic increase in mortality rate with level of ozone, ranging from 41.8 per 100,000 in the areas exposed to lowest ozone levels to 65.2 per 100,000 in areas exposed to highest ozone levels. This increase is statistically significant ($p<0.025$).

TABLE 4.—*Standardized Mortality Ratios (SMR) and Mortality Rates for Respiratory Disease by Level of Ozone, Adjusted for Age, Sex and Income*

*Ozone Level**	*Population*	*Deaths*		*Mortality*	
		Expected	*Actual*	*SMR*	*Rate/100M*
<20	260,514	109	90	82	41.8
20.0-22.4	412,156	264	242	92	46.5
22.5-24.9	587,836	428	433	101	51.4
25.0-27.4	589,459	196	219	112	56.6
27.5+	210,611	48	62	128	65.2

$\chi^2=11.86$, 4df, $P<0.025$

*90th percentile instantaneous daily maximum of ozone, pphm, 1961.

Sulfur dioxide. The distribution of 90th percentile IDM of sulfur dioxide (SO_2) is shown in Figure 3. Sulfur dioxide is produced largely by petrochemical plants in the southern extreme of the city and by power plants on the southwest coast. Sulfur dioxide is rapidly scavenged in the presence of oxidizing agents. It is not surprising therefore that the gradient of SO_2 concentrations is oriented from north to south almost directly opposite to that of ozone. Also note that the isopleths shown do not represent equal intervals. It is doubtful that the differences of 1 and 2 pphm

TABLE 5.—*Standardized Mortality Ratios (SMR) and Mortality Rates by Level of Sulfur Dioxide (SO_2), Adjusted for Age, Sex and Income*

SO_2 Level*	Population	Deaths Expected	Deaths Actual	Mortality SMR	Mortality Rate/100M
0-5	970,607	322	319	99	50.4
6-9	736,285	548	585	107	54.2
10-14	160,399	106	78	74	37.3
15-19	65,504	17	13	76	38.8
20+	127,781	54	51	95	48.3

$\chi^2 = 11.048$, 4df, $P < 0.05$

*90th percentile instantaneous daily maximum (1DM) of sulfur dioxide, pphm, 1961.

TABLE 6.—*Standardized Mortality Ratios (SMR) and Mortality Rates for Respiratory Disease by Level of Suspended Particulates, Adjusted for Age, Sex and Income*

Km Units DMHA*	Population	Deaths Expected	Deaths Actual	Mortality SMR	Mortality Rate/100M
Less than 10.5	441,107	255	207	81	41.2
10.5-11.4	326,978	234	241	103	52.2
11.5 or greater	256,746	228	244	107	54.3
Data not available	1,035,745	329	354	108	54.7

Partitioned $\chi^2 = 9.53$, 2df, $P < 0.01$ (first 3 groups only)

*Km units, 90th percentile daily maximum hourly average, 1961.

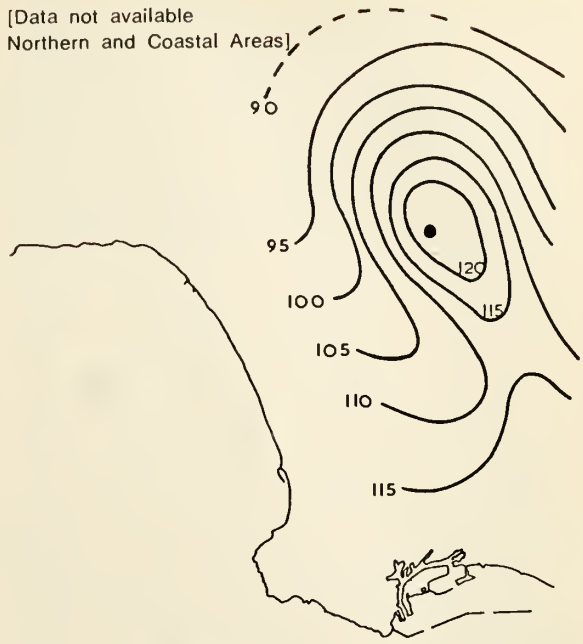

Figure 4.—Isopleths of 90th percentile daily maximum hourly average of suspended particulates (Km units × 10), 1961. Dot shows position of Civic Center.

shown in the northern part of the city are of any clinical significance.

Mortality by SO_2 level is shown in Table 5. Most of the city population lives in areas exposed to 10 pphm or less. At higher levels of SO_2 ranging to values above 25 pphm, however, there is no increase in mortality apparent. The three groups exposed to SO_2 levels above 10 pphm taken together show slightly fewer deaths than expected on the basis of their age, sex and income characteristics. There is nothing in these data to show that mortality is at all related to level of sulfur dioxide. It must be pointed out, however, that a very large trend of increase in mortality is associated with ozone, and is oriented in the opposite direction. Differences in mortality with level of sulfur dioxide would have to be quite large in order to be discovered by this method.

Suspended particulates. Instantaneous measurements for particulates cannot be obtained by the filtration methods current in 1961; daily maximum hourly averages (DMHA) are used in their place. Particulate data for 1961 are quite deficient for the purposes of this study because only six measuring stations collected particulate data for the entire year, and all of these were located in the central and south-central areas of the city. A partial data set therefore was used, with the coastal and San Fernando Valley areas excluded because of missing data. The distribution of 90th percentile DMHA of Km units is shown in Figure 4. Concentrations of suspended particulates are highest in the downtown area, and decline in all directions away from the downtown area. They do not appear to conform at all to the wind model.

Reliable particulate values are available for 365 tracts located in and around the central area. About half of the white population, or about 1 million people, live in these tracts. Areas excluded show slightly higher mortality rates than those included. Within the area for which particulate data are available there is a small trend of increasing respiratory mortality rates parallel to the gradient in levels of suspended particulates. This increase is statistically significant ($p < 0.01$). These data are shown in Table 6.

The peculiar distribution of suspended particulates pollution in concentric rings about the central city area gives some cause for concern, as the white population of this area is quite atypical in respect to some factors not well described by census data. The residents of skid-row districts are known for high mortality from many diseases, including respiratory disease. A brief sampling of those rubrics of the International Classification

of Diseases related to acute or chronic alcoholism shows a similar gradient in mortality (not statistically significant) by level of suspended particulates (see Table 7). There is no such gradient in alcohol-related deaths by ozone level. It can be argued that the gradient in respiratory mortality with particulate level may be related to the concentration of a special subpopulation of derelicts in the central city, and not to any specific effect of particulate air pollution.

Maximum temperature. The warmest areas of the city were identified by using long-term means of maximum temperature in July. Isotherms of July mean maximum temperatures are shown in Figure 5. There is a pronounced gradient of maximum temperature perpendicular to the shoreline, resembling the wind model over most of the Los Angeles plain but not in the western San Fernando Valley. It is not surprising there-

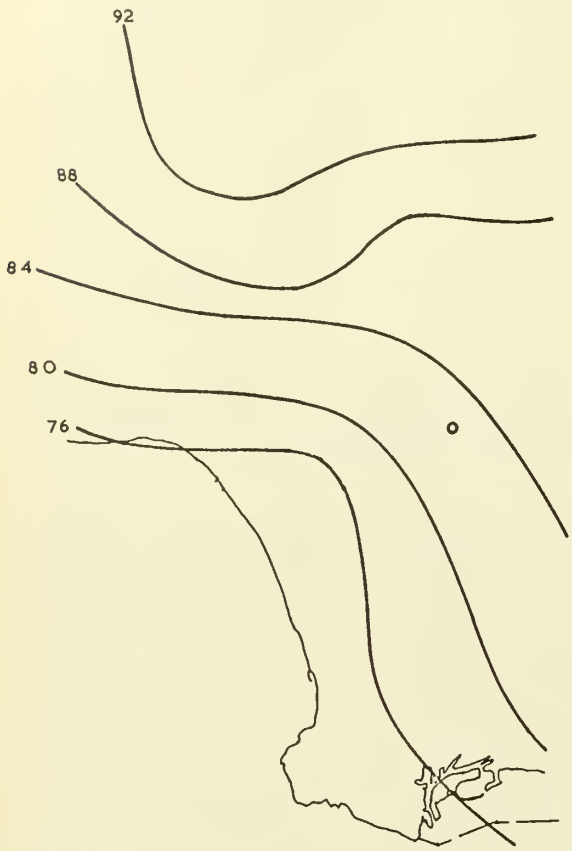

Figure 5.—Isotherms of July mean maximum temperature in degrees Fahrenheit. Circle shows position of Civic Center.

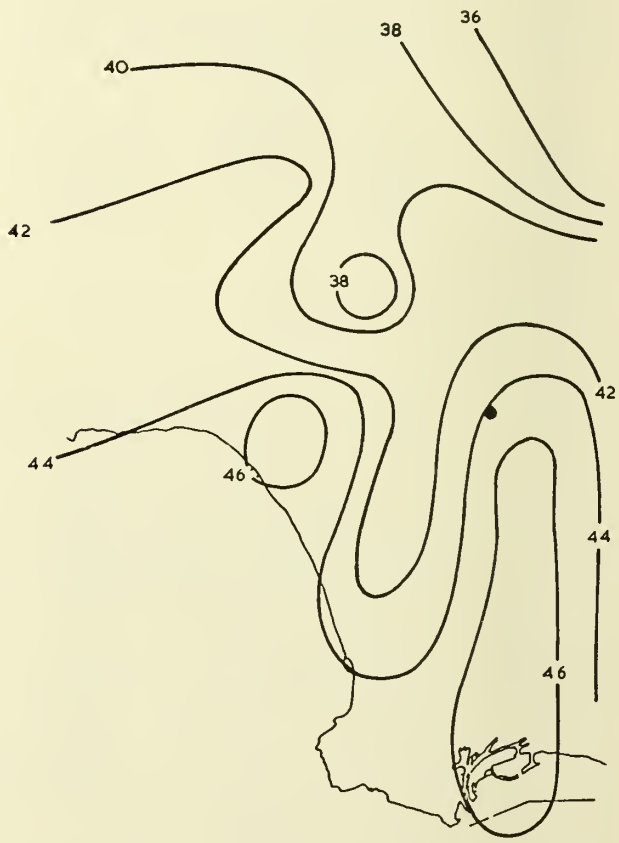

Figure 6.—Isotherms of January mean minimum temperature in degrees Fahrenheit. Dot shows position of Civic Center.

TABLE 7.—*Standardized Mortality Ratios (SMR) and Mortality Rates for Alcoholism-related Diseases,* by Level of Suspended Particulates. Data Adjusted for Age, Sex and Income*

Km Units DMHA†	*Population*	*Deaths*		*Mortality*	
		Expected	*Actual*	*SMR*	*Rate/100M*
Less than 10.5	441,107	122	108	89	23.0
10.5-11.4	326,978	114	118	103	26.7
11.5 or greater	256,746	135	144	107	27.6
Data not available	1,035,745	163	164	101	26.1

Partitioned $\chi^2=2.20$, 2df, $P>0.10$ (first 3 groups only)

*Sum of deaths due to International Classification of Diseases codes 280, 301.0, 301.1, 301.2, 311,0, 326.3, 462.1, 581, 587.0, 587.1.

†90th percentile daily maximum hourly average, Km units, 1961.

TABLE 8.—*Standardized Mortality Ratios (SMR) and Mortality Rates for Respiratory Disease by July Mean Maximum Temperature. Data Adjusted for Age, Sex and Income*

*Maximum Temperature**	*Population*	*Deaths*		*Mortality*	
		Expected	*Actual*	*SMR*	*Rate/100M*
Less than 80	622,795	299	253	85	42.9
80-83	597,018	477	491	103	52.2
84-87	355,271	143	144	101	51.3
88-91	370,028	99	127	129	65.4
92+	115,464	29	31	108	55.0

$\chi^2=15.9$, 4df, $P<0.005$

*July mean maximum temperature 1931-1952, degrees Fahrenheit.

TABLE 9.—*Standardized Mortality Ratios (SMR) and Mortality Rates for Respiratory Disease by January Mean Minimum Temperature. Data Adjusted for Age, Sex and Income*

Minimum Temperature*	Population	Deaths Expected	Deaths Actual	Mortality SMR	Mortality Rate/100M
Less than 42	824,639	384	389	101	51.4
42-43	664,928	348	334	96	48.7
44-45	388,045	237	240	101	51.5
46+	182,964	77	83	107	54.4

$\chi^2 = 1.05$, 3df, $P >> 0.10$

*January mean minimum temperature 1931-1952, degrees Fahrenheit.

fore to see in Table 8 that there is a suggestion of a gradient in respiratory mortality from coolest to warmest areas of the city. Although differences between areas are highly significant ($p < 0.005$), the gradient is quite irregular and the very warmest area shows death rates considerably lower than in the next warmest area. It is difficult to make any firm judgment about maximum temperature on the basis of such an unsystematic relationship.

Minimum temperature. Because cold weather has been said to contribute to respiratory deaths, January minimum temperatures were similarly examined. The distribution of January mean minimum temperature is shown in Figure 6. Because of unusual patterns of air movement on coldest days, this distribution varies greatly from the distribution of maximum temperature and does not resemble the wind model at all. Minimum temperatures are of course quite high in relation to most other United States cities, but there is a difference of 8 to 10 degrees between different parts of the city. Mortality rates at various levels of January mean minimum temperature appear in Table 9. There is no significant difference in mortality by minimum temperature apparent.

Discussion

The results of these analyses include four basic findings.

- There is a systematic spatial association between respiratory mortality and the distribution of 90th percentile IDM of ozone in the city of Los Angeles.
- There is a systematic spatial association between respiratory mortality and the distribution of 90th percentile DMHA of suspended particulates in those central city areas of Los Angeles where particulate data are adequate for analysis.
- There is irregular spatial association of respiratory mortality with maximum temperature.
- No spatial association of respiratory mortality with minimum temperature or sulfur dioxide has been shown to exist.

The spatial correlation of respiratory mortality with the distribution of ozone is most provocative. This finding is consistent with the observations of Sterling's group[6-8] that daily hospital admissions are related to oxidant levels. Numerous animal experiments and human exposure studies as reviewed by Jaffe[11] have shown that disturbances in pulmonary function and anatomical changes can be directly attributed to ozone toxicity. The correlation of mortality with particulates is equally interesting, and is consistent with findings in other studies linking particulates to lung disease.[12] The differences in respiratory mortality rates shown in results of this study are certainly consistent with a direct effect of these pollutants on community health. One should be cautious, however, in making these interpretations of direct causality without further evidence to rule out other epidemiologic factors that might lead to a spurious association.

The observed association of respiratory mortality with ozone is not an artifact of different age and sex distributions within the study population. Most of such an effect would be removed by the procedures for indirect age and sex adjustment employed in the study. Subsidiary analyses show that increases in respiratory mortality are concentrated in lower income groups, are almost wholly confined to males and increase radically with age in all income groups as ozone exposure increases. These observations argue against bias due to possible geographic differences in diagnostic practices and against geographic differences in ethnicity within the white population. Differences in mortality attributable to such factors should assort equally between the sexes.

Other sex-linked or socioeconomic status-conditioned factors, such as systematic regional differences in smoking patterns in different parts of the city, could produce mortality differences similar to these. Such regional biases are conceivable but not likely. Other possible sources of spurious association of mortality with ozone might be other environmental variables cross-correlated with ozone, such as nitrogen oxides or sulfur oxides. These are unlikely candidates for spurious association, since both are known respiratory irritants, and in a spatial sense are negatively correlated with oxidant in Los Angeles.

Increases in respiratory mortality correlated

with the distribution of particulates are consistent with the findings of other authors, who ascribe them directly to particulate air pollution. One must caution, however, that this observation of increased mortality correlated with particulate air pollution in Los Angeles directly parallels the findings of Winklestein's similar studies[12,13] in Buffalo. Winklestein felt particulates caused the increase in respiratory deaths. His study groups, however, may have contained bias related to differential distribution of working-class immigrant populations, who might drink more heavily than other ethnic groups. In Winklestein's data one finds a constant association among particulate air pollution, excess respiratory mortality and excess mortality from diseases related to chronic alcoholism. This same constellation of findings is present in Los Angeles. Since chronic alcoholism is generally associated with respiratory disease, and the skid rows of both cities are located in areas of high particulate air pollution, the two factors are inextricably confounded. It would take the wisdom of Solomon to determine whether particulates, alcoholism, or both, are responsible for this particular finding.

The regular spatial association of mortality with maximum temperature that was observed is difficult to evaluate, since there is a strong spatial correlation between maximum temperature and oxidant ($r = 0.876$). This spatial confounding of oxidant and maximum temperature repeats the temporal confounding problems encountered by previous authors.[1-5] An adequate statistical separation of these two elements has not yet been achieved in Los Angeles either in a spatial or a temporal sense. In this study the association of mortality with oxidant appears more persuasive than that with temperature. In a larger sense, however, the interpretative problems raised by repeated statistical confounding may be moot; the double association of temperature and ozone with mortality may be an expression of a synergistic action suggested elsewhere by laboratory studies.[14]

Lack of association between respiratory mortality and sulfur dioxide levels is not surprising because during this period SO_2 emissions were extremely well controlled in Los Angeles. Insufficient data were available to study any synergistic relationship of SO_2 *and* particulates with respiratory disease, or to evaluate the effect of particulate sulfates.

Because of the many possible confounding variables, it would be premature to conclude that the observed differences in mortality from respiratory disease are necessarily due to oxidant or particulate air pollution. The findings are consistent, however, with the observations of Sterling's group[6-8] that daily hospital admissions for respiratory disease are correlated with both oxidant and particulate matter. These results clearly indicate the need for further inquiry into the possible relation between air pollution and respiratory disease in Los Angeles. Further studies should make use of superior epidemiologic, demographic and air pollutant data available during the 1970 pericensal period in order to better answer the question "Is oxidant air pollution a significant health hazard in Los Angeles?"

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Refer to: Edwards WM Jr: Acupuncture in Nevada, second report (Government and Medicine). West J Med 124:167-168, Feb 1976

The State of Nevada has now given its fourth series of acupuncture licensing examinations. In all, 62 candidates have taken examinations. Licenses have been granted to 27 persons as master acupuncturists (Doctors of Traditional Chinese Medicine or Doctors of Acupuncture) and to 6 as Acupuncture Assistants. At present, 4 acupuncturists practice in the Reno area and 13 in Las Vegas.

Acupuncture in Nevada, Second Report

WILLIAM M. EDWARDS, JR., MD, MPH, *Carson City*

SINCE THE previous article on acupuncture in Nevada appeared in the JOURNAL,[1] licensing procedures by the Nevada State Board of Oriental Medicine have been strengthened and are operating smoothly. Examinations of candidates are given in the first week of May and in the first week of December each year.

The Nevada Oriental Medicine Act requires that an applicant must have had a minimum of three years of formal training in acupuncture and Oriental medicine in addition to ten years in practice before taking the examinations for a license as a master acupuncturist (Doctor of Traditional Chinese Medicine or Doctor of Acupuncture). Being licensed as an MD or a DO does not automatically qualify a person for a license from this board.

The current position of the Nevada State Board of Oriental Medicine is that medical doctors who are properly trained in acupuncture may use it as one method of treatment in their medical practice without additional licensing from the Board. However, under the Oriental Medicine Act, a physician who represents himself to the public as an acupuncture specialist is required to first be licensed as a Doctor of Traditional Chinese Medicine or a Doctor of Acupuncture by the State Board of Oriental Medicine, meeting all the pertinent requirements of law and regulation.

Licenses are granted in four categories: Doctor of Traditional Oriental Medicine, Doctor of Acupuncture, Doctor of Herbology and Acupuncture Assistant. To be licensed as a Doctor of Traditional Oriental Medicine, a candidate must have achieved passing grades in both acupuncture and herbology examinations. As yet, no one has been licensed merely as a Doctor of Herbology.

The State of Nevada has now given its acupuncture licensing examinations four times. A total of 62 applicants have been tested. Of these, 27 have been licensed as Doctors of Traditional Chinese Medicine or Doctors of Acupuncture and 6 as Acupuncture Assistants. There are 4 acupuncturists in practice in the Reno area and 13 in Las Vegas. All are of Oriental extraction.

The application fee to take the examinations is $100. An investigative fee deposit of $300 is also required at the time an application is submitted. Candidates must pay all expenses for the investigations of their background and training. Qualifications are carefully checked by the Board.

Examinations take three days in all. The written

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portions are make up of true-false and multiple choice questions and are given in the language of the applicant's choice. Candidates must pay translation costs if translations are required. Applicants may take the examinations only three times in any five-year period. The first day's examinations are entirely written and cover basic science questions. Included are questions on anatomy, physiology, chemistry, bacteriology, pathology, first aid and hygiene. The herbology section of the test is given on the afternoon of the first day. The second day consists of morning and afternoon examinations (also written) on acupuncture and traditional Oriental medicine. The third day is taken up by practical and demonstrative examinations, oral questions and evaluations of fluency in the English language—the Nevada Board of Oriental Medicine requires fluency in spoken English for master-level licenses.

The Board contracts with Dr. Thomas M. Cassese, a Professor of Education at the University of Nevada, Las Vegas, who, for a consulting fee, assembles the test questions into examination form, administers the tests and provides the Board with an evaluation of test results. Between 400 and 700 questions are used in each series of examinations. Testing procedures now have become quite well established. Members of the Board of Oriental Medicine evaluate the candidates' English-speaking abilities but otherwise do not participate in administering the tests. Licensees may submit additional questions to the pool of test questions maintained by Dr. Cassese. Licensees, on request, participate and assist in testing candidates during the demonstration portions of the examinations. The Board does not give out samples of examination questions and copies of examinations are carefully guarded because the pool of questions from which examinations are taken has not been easy to develop.

Candidates for licenses as Acupuncture Assistants are required to have had a minimum of three years of training and three years of experience in the practice of acupuncture in order to take the examinations. Candidates for master-level licenses who pass the examinations but who lack ability in spoken English are licensed as Acupuncture Assistants until such time as they are able to meet the Board's requirements for proficiency in English.

The provision in the Oriental Medicine Act allowing acupuncturists with 20 years of experience to be licensed without taking examinations was set aside by the Board of Oriental Medicine at its first meeting, May 15, 1973, and therefore no one has been granted a license under a grandfather clause. The word "may" in the Act gave the Board the option to take this action. All applicants for license are required to take the Board's examinations.

The Nevada State Legislature, which meets only every other year, passed the Chinese Medicine Act in 1973 allowing nonphysician acupuncturists to practice in Nevada. The 1975 Legislature, now adjourned, made only minor changes in the law: the name Chinese Medicine was changed to Oriental Medicine and under A.B. 26 —which passed the Legislature and was signed into law by Governor Mike O'Callaghan—it was mandated that all health and accident insurance policies sold in Nevada after July 1, 1975 must provide coverage for treatment and services carried out by licensees of the Nevada State Board of Oriental Medicine.

At present there are no accredited schools or colleges of oriental medicine in Nevada. (To our knowledge the establishment of one such school is possibly being contemplated at this time.) In this regard the Nevada statutes read as follows: "A school or college of Oriental medicine may be established and maintained in this state only if (a) Its establishment is approved by the Board, (b) Its curriculum is approved annually by the Board for content and quality of instruction in accordance with the requirements of this chapter . . . The Board may prescribe the courses of study required."[2] No money has been voted by the Legislature for such a school and if and when one is established it would necessarily have to be private.

In a number of other states there continues to be public pressure for laws that will legalize acupuncture and the practice of Oriental medicine. The Nevada experience continues to appear to be a satisfactory method of handling the issues and problems involved in licensure and control. (It might be noted that in Montana, which also has an acupuncture licensing law, several persons have been licensed to practice acupuncture by virtue of their Nevada licenses.)

The Nevada Board of Oriental Medicine will continue to follow acupuncture practice and report on it regularly.

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Refer to: Ricketts DW: Jury verdicts and the medical malpractice insurance crisis (Informed Opinion). West J Med 124: 169-171, Feb 1976

Informed Opinion

Jury Verdicts and the Medical Malpractice Insurance Crisis

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EDITOR'S NOTE: *The author is an attorney whose firm does a substantial amount of malpractice work.*—MSMW

OF 80* jury verdicts rendered in medical and dental malpractice cases in the Central District of Los Angeles County, 37 verdicts were for the plaintiffs in the amount of $5,861,046. A settlement could have been effected in many of these 37 cases which would have reduced the payout by $1,522,046. This suggests a cause for the medical malpractice insurance crisis that has been overlooked.

The crisis has been framed as a battle between doctors and lawyers. The arguments are, by now, familiar and need not be repeated. But it is fair to ask whether physicians should be pointing their fingers at attorneys and vice versa. Has each side correctly identified the opposition and the cause of the crisis?

There is a third party that benefits greatly from this struggle and who, it can be argued, is the real villain—the insurance industry. The cause of the crisis is not jury verdicts and contingent fee contracts nor is it the negligence of doctors. Juries render verdicts and attorneys receive contingent fees in all personal injury cases and a portion of the defendants in all personal injury cases commit negligence. Why then, a "medical malpractice crisis" and not a "personal injury crisis"? More to the point, assuming the protestations of unprofitability to be true, why *is* it unprofitable for insurance companies to write medical malpractice insurance?

The insurance carriers have argued that one of the principal causes for the alleged unprofitability, and the necessity for charging large premiums to physicians and hospitals for coverage, is runaway jury verdicts. To test the truth of the argument requires an understanding of why cases are tried (with resulting verdicts) and not settled. Trials occur for one of two reasons. First, and most obvious, a case is tried when the defendant does not feel that there is any liability and is unwilling to make any offer (other than, perhaps, a nuisance or cost-of-suit settlement). When this occurs, the plaintiff must either dismiss the case or try it. Trial invariably results. The second trial situation arises when the defendant *does* recognize his liability and *does* make a substantial offer to settle, but is turned down by the plaintiff.

A cursory look at the jury verdicts in this study supports the argument of the insurance carriers, if it is assumed that they are always correct in predicting the outcome of trials. As shown in Table 1, the carriers made no substantial offer in 47 of the 80 cases, yet in 17 of these cases the juries returned verdicts totaling $2,853,962. On the other hand, the carriers did make substantial offers totaling $519,200 in 13 cases but received defense verdicts. If, however, the infallibility of insurance carriers is rejected, no firm conclusion can be drawn from the raw figures. They can be

*The survey period was from May 30, 1972, to February 2, 1975. Statistics for seven weeks were not readily available. Information was available for 87 cases but was not complete for six and one other case resulted in a hung jury. These were excluded from the survey. One case resulted in a verdict for plaintiff of $1. This was included as a defense verdict. Another case resulted in a verdict of $1,000,000 but was reduced by the trial judge in a posttrial motion. It is included in the survey figures as a $1-million verdict.

Reprint requests to: Donald W. Ricketts, 3303 Wilshire Boulevard, Suite 600, Los Angeles, CA 90010.

TABLE 1.—*Offers, Demands and Verdicts in Malpractice Cases*
Los Angeles County Superior Court, Central District, May 30, 1972-February 2, 1975

Offer/Result	*Number of Cases*	*Total Offers*	*Total Demands*	*Total Verdicts*
No substantial offer, defense verdict	30	$ 23,000	$ 940,000	$ 0
No substantial offer, plaintiff's verdict	17	9,000	2,350,000	2,853,962
Substantial offer, defense verdict	13	519,200	1,073,000	0
Substantial offer, plaintiff's verdict	20	985,000	1,989,000	3,007,084
TOTALS	80	$1,536,200	$6,352,000	$5,861,046

used to argue either that the juries have run wild or that the insurance carriers are not predicting with reasonable accuracy what a jury will do with a given case.

It is reasonable to assume that juries sometimes do less than justice. Any system administered by men will have some error. The problem is determining what amount of jury verdicts can be considered to be unreasonably excessive, if any. This of course is problematical. Attorneys who regularly deal with personal injury cases frequently differ on the fair value of cases. (This is of course a very good reason for preserving the jury system.) But if the reasons why cases are tried and not settled are borne in mind, a fair analysis can be made.

Thirty-seven of the 80 cases in the survey resulted in verdicts for the plaintiffs. In 20 of these the defendants made substantial offers, indicating that they felt that a verdict for the plaintiff was proper but that the only true area of disagreement was the amount to be paid. In five of these cases the verdict fell between the amount the defendants had offered and the amount the plaintiffs had demanded to settle. Two others fell below the amount of the offer. It is generally considered that if a verdict falls between the amount of the offer and the demand, it is "in line." The total of these seven judgments ($268,911) therefore can be subtracted from the $5,861,046 total, leaving $5,592,135 to be considered.

Of the remaining 13 cases (of the 20 in which the defendants made substantial offers) the total judgments were $2,738,173, the defendants had offered $882,000, and the plaintiffs had demanded $1,311,000. Inasmuch as these were cases in which the defendants were willing to pay substantial sums to settle, by no stretch of the imagination can the *total* of the verdicts be considered excessive. Clearly, the amounts the defendants indicated they would pay would be the minimum reasonable verdict. But the plaintiffs' attorneys in these cases would argue that their demands were closer to the verdicts and were thus more realistic and a better approximation of the fair value of the cases. There is a third school that holds that the fair value of a case is what a jury says it is and that therefore no amount of these verdicts should be considered excessive. While not necessarily agreeing with this last proposition, it is the appropriate rule to be applied here.

The defendants recognized (by making substantial offers) that these were cases in which they were liable. With that proposition settled, it became incumbent on the insurance companies to realistically evaluate the cases. They did an extremely poor job, missing the jury verdicts by $1,856,173. Plaintiffs' lawyers were much more realistic, and in any event gave the insurance companies the opportunity to settle these cases for $1,427,173 less than the verdicts. The function of attorneys and insurance companies in litigation is to realistically assess the risk—the exposure—their clients face at the hands of a jury. In these cases the insurance carriers had the opportunity to settle at reasonable figures and did not do so—either because of errors of judgment or vindictiveness. They should not now be allowed to ignore their bad judgment and complain that juries are not agreeing with it. They should not be allowed to complain that any portion of this $2,738,173 in verdicts is excessive. Deducting this sum from the remaining total of $5,592,135 leaves $2,853,962 to be considered.

This sum is accounted for by those 17 cases in which the plaintiffs received a verdict and the defendants did not admit that they were liable by making a substantial offer. Let us concede, for the sake of argument, that in rendering a portion of these verdicts in favor of the plaintiffs the juries committed some error.

Insurance companies are quick to argue that juries commit error in rendering verdicts against them. Fairness would seem to dictate that they should also concede that juries commit error by

rendering verdicts in their favor. In the 43 cases where verdicts in favor of defendants were rendered, the insurance companies made substantial offers in 13 of them. If the judgment of the insurance companies was sound in making these offers, the juries in rendering defense verdicts erred 30 percent of the time. It would seem to be proper, then, to conclude that the juries also erred 30 percent of the time in rendering verdicts for the plaintiffs. Translating this into dollars, of the $2,853,962 in verdicts arguably erroneously assessed, in fact only $856,188.60 of the total amounts awarded can be *assumed* to be excessive. However, it would also be fair to balance out the juries' "mistakes" subtracting from the amount "erroneously" awarded to plaintiffs, the amount "erroneously" saved for the insurance carriers by those cases in which the defendants had made substantial offers but received defense verdicts. The offers in these cases were $519,200 which, subtracted from the $856,188.60 assumed to be excessive, leaves $336,988.60.

A "net error" of approximately 6 percent can hardly be considered unreasonable. The jury system should not be used as a whipping boy by the insurance carriers to cover up their own errors of judgment. The answer to the medical malpractice crisis is not legislation limiting the rights of plaintiffs nor is it increased premiums for malpractice coverage. The answer lies in a thorough review by the insurance companies of their procedures for evaluating and settling claims.

CORRECTION

In the Medical Staff Conference "Pericarditis," which was in the December 1975 issue, the legends for three of the figures were incorrect as they appeared. The legend for Figure 4 should have read "Electrocardiogram of a normal young man." The legend for Figure 5 should have read "Electrocardiogram of same person as in Figure 4 following exercise." The legend for Figure 6 should have read "Late pattern of pericarditis."

Refer to: Schmerl EF, Steiner P: Porthole ulcers associated with gastric intubation (Medical Information). West J Med 124:172-173, Feb 1976

Porthole Ulcers Associated with Gastric Intubation

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PAUL STEINER, MD
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On geriatric hospital wards, nasogastric tube feeding has become a common routine bedside measure. Among the 90 inpatients on our service there may be as many as 20 at any one time in whom long-term nasogastric intubation is being used.

Because of its usefulness and its benefits, one is inclined to overlook the fact that this technique is indeed an invasive procedure and that a large portion of the indwelling tube used remains out of visual control. Considering this, the relative safety of the technique is quite remarkable.

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This study was supported by a grant from the Professional Fee Fund of the Alameda County Medical Staff.

Reprint requests to: Egon F. Schmerl, MD, 333 Scenic Avenue, Piedmont, CA 94611.

This report deals with a type of tube-induced gastric ulcer that we observed in patients in whom nasogastric feeding was being used. These cases occurred before 1966, when one of us (E.F.S.) began to use a modified bedside technique. During eight years of follow-up, among a hospital total of 1,045 autopsies, we have found no more evidence of gastric intubation ulcers. Recently, however, they have been reported elsewhere.[1] Their consistent absence on our wards has led us to the conclusion that our modification, and the hypothesis on which it is based, has enough merit to be reported.

Report of a Case

The patient was a 64-year-old woman who had had diarrhea, vomiting and abdominal pain for four weeks before she was admitted to Fairmont Alameda County Hospital on April 18, 1966. Her height was 4 feet 9 inches and her weight was 240 pounds.

The previous medical history included two gallbladder operations and an appendectomy. The patient was described as grotesquely obese, pale, lethargic and tachypneic. Pulse rate was 120 per minute, blood pressure was 110/70 mm of mercury. In the past, the patient had been taking sodium salicylate for arthritis, and chlorothiazides for excessive fluids. Infiltrations in right middle and left lower lobes were noted on x-ray studies. Leukocytosis was present. The leukocyte

Figure 1.—Antrum of the stomach. Three of the four ulcers are in linear arrangement.

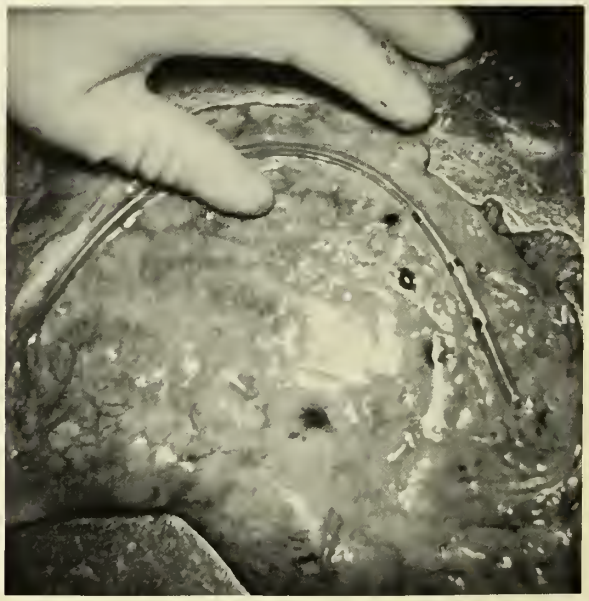

Figure 2.—A nasogastric tube is held to show the space relationship of three ulcers to the portholes.

Figure 3.—Nasogastric tube is held in place by a strip of umbilical tie. The knot permits short gliding shifts of the tube. Tape is out of the way.

count was 15,000 per cu mm with 7 percent banded forms. A clinical impression of dehydration corresponded to laboratory findings: serum chlorides were 86 mEq, potassium was 2.7 mEq.

On April 21, potassium was 4.5 mEq, serum chlorides had fallen to 77 mEq and sodium to 105 mEq. Blood urea nitrogen was 45 mg per 100 ml. A nasogastric tube had been inserted shortly after admission. On April 21, small amounts of material resembling coffee grounds were noted. The patient's general condition worsened and, despite supportive measures, she died on April 21. During her last six hours, 100 ml of gastric content was obtained by aspiration.

Findings on autopsy included acute pulmonary embolism due to phlebothrombosis of the deep veins of the left leg, pulmonary infarcts in right upper and lower lobe, intubation ulcers of stomach and arteriosclerotic cardiovascular disease. The stomach was described as follows: "The wall of the front antral part of the stomach shows four shallow, black ovoid ulcers each measuring 5 by 8 mm. Three of these ulcers are in one straight line running approximately in the direction from the esophagus to the pylorus" (see Figures 1 and 2). Findings in the gastrointestinal tract were otherwise not remarkable.

The location, linear arrangement and spacing of the three ulcers (Figure 1) suggest a causal association with gastric intubation (Figure 2).

Discussion

It is common usage to secure feeding tubes in place by taping them to the patient's nostril. This, we propose, may contribute to the hazard of ulceration because it locks the tube as well as its portholes facing the gastric mucosa in a nearly fixed position. When suction occurs, the same tiny areas may be exposed consistently to the hydraulic action at the site of the portholes, which then act like valves. This is important not only when the purpose of intubation is suction, as for decompression, but in long-term tube feeding. In the latter instance, the valve-like portholes are also apt to attract gastric membrane: during meals, in order to ascertain good positioning and patency, or to remedy clogging, it is often necessary to aspirate with a syringe. Then suction may force gastric mucosa, especially redundant and loose along the magenstrasse, into the portholes. In addition, when the outer upper end of the feeding tube is clamped between meals, and residual tube content escapes into the stomach, a relative vacuum in the tube (which incidentally can be shown *in vitro*) is likely to attract mucosa. These hazards should be kept in mind especially on a geriatric ward where anemia from gastric blood loss may easily remain undetected in those patients who are debilitated and malnourished.

In view of this, we use a technique that allows such a tube some leeway to slide. Moreover, nursing personnel have been trained to move the tube slightly from time to time. This is made possible (as shown in Figure 3) when a piece of umbilical tie is knotted around the tube instead of using adhesive tape to secure the tube to the nostril. This tie holds the tube in place yet it permits slight changes of position. The two ends of the tie reach across the patient's cheeks and, by means of a small loop, the ends are taped in front of the ears. Variances here minimize skin irritation. Compared with nostril taping, this technique happens to be rather sanitary. Cosmetically, there is an esthetic "fallout": When the nose is made unsightly with tape it tends to disfigure the whole face. On long-term wards we have found that this affects roommates and visitors as well as the attitude of ward personnel. It is to be noted that, during eight years of observation, the sliding feature has caused no undesirable major slippage.

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Refer to: Ferguson JM, Wermuth BM, Taylor CB: Rapid desensitization of a needle phobia by participant modeling (Medical Information). West J Med 124:174-176, Feb 1976

Rapid Desensitization of a Needle Phobia by Participant Modeling

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PATIENT FEARS OF minor operative procedures such as blood drawing and intravenous administration of fluids and medications are often troublesome. When these fears are of phobic proportions and when the feared behavior is a prerequisite for a major surgical operation, the ensuing struggle can become a life-threatening test of will. On occasion, this lack of cooperation can be sufficient to postpone or cancel a necessary operation. In these situations, the traditional use of reassurance is often ineffective. If a patient is subdued physically or chemically before an operation, the danger remains that this might cause pronounced fear and irrational behavior postoperatively. At best, an angry patient may have to be restrained during these procedures.

Phobias or intense fears have traditionally required considerable therapist time for successful treatment. The more recent behavior therapy approaches of systematic desensitization,[1] flooding[2] and implosion[3] have reduced this time requirement considerably. Bandura and co-workers[4,5] have developed a participant modeling approach to phobias that further reduces the amount of time needed to eliminate irrational fears, and eliminates the need for a trained psychotherapist.

Bandura's basic premise is "successful performance is the primary vehicle of psychological change."[6] To facilitate approach to the feared object and performance of the dreaded task, the therapist arranges the patients' environment in such a way that they are able to overcome their fears one small step at a time. With the aid of demonstration or modeling by a therapist, a patient is able to rapidly progress to having a feared activity carried out.

The steps in participant modeling are:

- *Instruction*—the patient is given information about the feared object or its feared qualities in a way that shows that the fear is excessive or unrealistic. At the same time, a description of the desensitization procedure and the positive expectation that the procedure will work without inducing undue anxiety are given to the patient.
- *Response modeling*—the therapist handles the feared object and interacts with it in a way to show that the irrational component of the patient's fear is unfounded.
- *Joint performance with the therapist*—the patient is encouraged by the therapist to join with him in a series of interactions with the feared object starting with situations that provoke relatively little anxiety and ending with accomplishment of the feared activity. These substeps or response induction aids can be progressive physical approaches to the final task, increased length of time exposed to the feared object, inclusion of protective devices (for example, gloves) and exposure to a series of related but much less fear-inducing objects (for example, smaller needles).
- *Self-directed practice*—the patient is encouraged to practice his new skills or fearlessness alone and in varied settings to ensure that he does not attribute his sudden bravery to either the therapist or the therapeutic situation.

Information alone is sufficient to allow some patients to carry out their feared act. For others, seeing a therapist model or act out the feared situation will reduce fears sufficiently for their own participation. Still other patients need to have a battery of response induction aids or substeps in the desensitization process carried out with the help of the therapist to enable them to engage in their feared behavior.

The danger in this form of therapy is the possibility of enhancing patient fears by making de-

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mands too early to carry out the feared activity. Excessive or premature demands can undermine a patient's self-confidence, reinstate fears that may have been partially eliminated or increase the intensity of fears. To avoid this, patients are asked if they are unduly frightened at each step in the desensitization process. If the answer is yes, the procedure is slowed or additional response induction aids are used.

The following case illustrates the use of participant modeling to eliminate a needle phobia in a surgical patient.

Report of a Case

A 23-year-old white woman was admitted to Stanford Medical Center for a staging laparotomy for Hodgkin's disease. Although she understood the necessity for the operation, she cried, screamed and pulled away when approached by anyone with a hypodermic needle. Despite several hours of pleading and exhortation by the house staff and nurses, she would not allow blood to be drawn or an intravenous catheter to be placed. Because of the patient's resistance the operation was postponed indefinitely.

History

The patient reported having been terrified of needles as a child and reacting to all injections by crying. At age 13, an acute allergic response developed after an injection of penicillin and the patient lost consciousness. Although at age 18 she was able to tolerate blood drawing during a miscarriage of her first pregnancy, at age 20 during her second delivery she became acutely hysterical when an intravenous catheter was started and demanded its immediate removal. The patient was able to undergo a series of allergy shots over a 20-week period at age 22, but when Hodgkin's disease was diagnosed six months before the present admission, she began to experience an extreme fear of needles. The initial lymph node biopsy was conducted under general anesthesia. The patient was so fearful about this procedure that the anesthesiologist decided to start the intravenous administration of anesthetic after she was unconscious and remove the catheter before she awoke.

The patient has no other significant psychiatric symptoms. She appears to be an energetic, intelligent, sensitive young woman with an isolated fear of hypodermic needles and intravenous equipment.

Therapy

The process of phobia desensitization through participant modeling was briefly described to a psychiatry resident who had no earlier experience with this type of therapy. After a five-minue description of the procedure, the therapist met the patient on the surgery ward and obtained a brief history of the present disorder. He ascertained that the patient desired the staging laparotomy and treatment for Hodgkin's disease. He explained the process of desensitization briefly and told her it would take approximately an hour, during which she would be asked to touch and experiment with some of the intravenous equipment, syringes and needles. She was told that after this hour she would feel more comfortable with these items.

A Mayo stand with packaged tubing, syringes, tape, novocaine, gauze squares, alcohol, needles, several medication vials and a tourniquet was placed in the patient's room along with an intravenous apparatus pole. The patient was asked to sit as close to the assembled medical equipment as she felt comfortable, a distance of about three feet. The therapist picked up the packaged materials one at a time, identified them and handed them to the patient, each time pausing until she was comfortable touching the packages. The patient was asked to remove the articles from the packaging, which she did very slowly. She helped the therapist connect the intravenous tubing to a bottle and hang it from the intravenous apparatus pole. The therapist then put an unexposed needle on a syringe, held it for a moment and handed it to the patient. She held the needle and syringe and looked at them until she felt comfortable. At this point, the therapist removed the cover from the needle. When she no longer felt anxious holding the syringe with a bared needle, the therapist touched the needle to his own skin and held the needle between his fingers. The patient was able to copy these actions and she progressed to rubbing the needle on her own arm and back of her hand. The hypodermic needle was taped to the back of her arm and left there for her to experience the feeling of a needle touching her skin.

The therapist put a needle on a second syringe and filled it with procaine. The patient held the medication-filled syringe until she felt comfortable. The therapist then injected procaine into an orange and asked the patient to copy his actions. She was able to inject the orange several times

without undue anxiety. At this point the patient and the therapist interviewed a second patient who had an intravenous catheter in his arm. She asked him some questions about how it felt and then watched the therapist remove the catheter. She was then handed a tourniquet which she handled until she was comfortable. After the tourniquet was applied to her arm, her veins were identified and touched by both the therapist and the patient. Her skin was cleansed with alcohol and procaine was injected over a vein with a 25 gauge needle. The patient was asked to look at the small needle as it remained in her skin and watch as it was removed. Finally, a Medicut® intravenous catheter was inserted into the patient's vein without objection while she looked away. She was asked to look as the catheter was taped in place and watch while the tubing was connected to a bottle of 5 percent solution of dextrose and water.

Approximately an hour was needed for the entire procedure. The patient and the therapist talked about the catheter being in place and about the necessity for having experience with the whole apparatus to feel comfortable with it. She was encouraged to walk around the room with the apparatus (including a pole) and then asked to take a tour of the hospital pushing the pole with her. After her walk, which lasted about an hour and a half, the catheter was removed and the patient scheduled for surgical operation later in the week.

On the day of operation the patient tolerated multiple blood drawings and the placement of several intravenous catheters and needles both before and after operation without incident. The patient reports a sense of pride in her accomplishment and feels more relaxed in the surrounding of a hospital. She has a much better attitude toward the operation, her doctors and her illness than she did before the desensitization procedure.

Discussion

This case illustrates the clinical application of a procedure described in the experimental psychology literature. When the procedure is used in actual therapy, the well-defined experimental steps merge. Information is collected and dispensed and expectations about therapy are established from the beginning. The patient was informed that the procedure would be brief, that she would have an active part in the therapy and that it would be successful. The various paraphernalia associated with starting and maintaining intravenous therapy were handled first by the therapist, with an appropriate explanation about their function, and then by the patient. She was allowed to become fully familiar with the materials. She handled the needle and syringe, felt the needle against her skin, stuck it into an orange and operated the syringe, and then shared her fears and experiences with other patients. She was involved in each step of the process as an active participant. Once the catheter was placed, she was encouraged to practice and experience the limitations of the apparatus by walking with it around the hospital.

The procedure was rapid and effective. There was no suggestion of a recurrence of her fears on the day surgical operation was carried out or substitution of any other symptoms. An added benefit of the desensitization was a general improvement in her attitude about operations, about her doctors and in her hopes for a positive outcome from the operation. At follow-up examination two months after operation, the patient noted a continuing lack of undue fear of needles and medical equipment.

Conclusions

Participant modeling was used to desensitize a patient with a long-standing fear of needles and intravenous apparatus in a short period of time. Although her therapist had not observed desensitization by participant modeling before involvement in this case, he was able to learn the technique and successfully desensitize the patient after only a few minutes of instruction. This is a therapeutic procedure that can be employed by members of the medical profession or health care team to rapidly overcome specific patient fears. In the case reported, use of this technique allowed a necessary operation to be carried out without undue delay.

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BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

HANDBOOK OF LEGAL MEDICINE—Fourth Edition—Alan R. Moritz, MD, Professor of Pathology, Case Western Reserve University, Cleveland; R. Crawford Morris, LL B, Partner, Arter & Hadden, Cleveland; With the assistance of Charles S. Hirsch, MD, Assistant Professor of Forensic Pathology, Case Western Reserve University. The C. V. Mosby Company, Publishers, 3301 Washington Boulevard, St. Louis, MO (63103), 1975. 286 pages, $10.25.

This paperback manual contains a 126-page section on the physician's legal responsibilities with regard to violent crimes and injuries (forensic pathology), and a 126-page section on the physician's liabilities and responsibilities in the civil law (legal medicine). It is a brief overview covering many subjects, and is divided into 44 chapters, some only a single page in length.

The law, unlike medicine, varies among the states, and any law book written for all the states must therefore generalize legal concepts and omit much information. This handbook presents only the broadest legal concepts, but does so in a direct and concise fashion, utilizing simple examples where necessary. An unfortunate complication, however, of the concise delivery is frequent use of legal "words of art" without adequate definition. A legal word glossary at the end of the book is of little help in this regard since the need for careful definition of seemingly common words is rarely obvious.

The brevity of this handbook may also mislead physicians. For example, chapter 40 appears to state that a patient can waive his right to sue a physician for negligence. This is untrue, but is probably a misinterpretation of the oversimplified statement that the right to sue can be signed away in an agreement to a money settlement. Another example is in chapter 21 where one form of comparative negligence is described while another form is omitted. Unfortunately, the omitted form is the law in California.

The section on forensic pathology contains less legal terminology and conceptual pitfalls than the section on legal medicine, and reflects the pathology background of the two physician authors. Interest in the subjects covered in this section should therefore be the primary reason for buying the book.

The *Handbook of Legal Medicine* is a useful quick reference source on both forensic pathology and legal medicine for physicians having substantial prior knowledge of the law, but may be incomplete and misleading for others.

DAN J. TENNENHOUSE, MD, JD

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PHYSICAL EXAMINATION OF THE SURGICAL PATIENT—An Introduction to Clinical Surgery—Fourth Edition—J. Englebert Dunphy, MD, Professor of Surgery, University of California, San Francisco; and Thomas W. Botsford, MD, Associate Professor of Surgery, Harvard Medical School, Surgeon, Peter Bent Brigham Hospital, Boston. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1975. 414 pages, $16.00

To beginning medical students, getting on the wards arouses intense feelings of interest and curiosity. Surgical wards in particular are susceptible to this enthusiastic invasion of clinical neophytes, as surgical patients so often harbor nice physical findings. But, because all patients are first and foremost *people* with a disease, the initial focus of this primer is psychological. Proper attention is paid to treating patients as people, to draping and talking to them in a way that they can relax, and to conducting the physical examination with "dignity, gentleness and thoughtfulness."

Naturally, the text emphasizes examination of patients with surgical disease—for details of the funduscopic examination the student is referred elsewhere. But those parts of the usual physical examination that receive short shrift in other texts are here well described: for example, the detection of peripheral vascular disease and herniae, as well as lesions of the scrotum, rectum and pelvis. As before, special attention is paid to the acute abdomen, the postoperative state and the musculoskeletal system.

Throughout, physical findings are given clinical meaning. For example, in the superb new chapter on the surgical cardiac patient, why the student should listen for the opening snap in mitral disease is explained—the snap implies a flexible valve and hence a "reparative rather than a replacement operation."

More than a guidebook on examination technique, this edition serves as a "stepping stone for the assumption of the responsibilities of a Senior Clinical Clerk." Accordingly, the last seven chapters elaborate how the approach to an acutely injured patient differs from the ordinary physical examination.

The result is a useful book that eases the transition from the basic sciences to clinical practice. As with previous editions, it distills "the stuff of which clinicians are made. Some of it is new; most of it is so old that it is in danger of being forgotten. All of it is important."

ALAN T. MARTY, MD

* * *

CEREBROVASCULAR DISABILITY AND THE AGEING BRAIN—G. F. Adams, CBE, MD, FRCP, Honorary Professor of Geriatric Medicine, Queen's University and Physician to Wakehurst House, City Hospital, Belfast; With Chapters on Aphasia and the Management of Major Strokes, and with excerpts from papers written by the late L. J. Hurwitz, MD, FRCPE, Consultant Neurologist to the Royal Victoria, Claremont Street and City Hospitals, Belfast. Churchill Livingstone, Edinburgh and London, 1974. Distributed in the USA by Longman Inc, 72 Fifth Avenue, New York City (10011). 156 pages, $16.50.

This short monograph has been designed for physicians to "encourage wider appreciation of the limitations imposed on capacity by age and disease." It briefly deals with the pathogenesis of neurological disability in ageing. It comments briefly about clinical evaluation of patients in terms of their intellectual and motor deficits. It outlines some of the common syndromes associated with stroke and dementia, and it briefly summarizes some general principles of management of patients with stroke. The book is replete with general principles but deficient in terms of dealing with specific neurological problems. It does not critically analyze the literature with regard to such complex issues as the indications for angiography, endarterectomy or anticoagulation. It has been published almost simultaneously with another British monograph, "Strokes: Natural History, Pathology and Surgical Treatment" by E. C. Hutchinson and E. J. Acheson (W. B. Saunders, Philadelphia, 1975), with which it does not compare favorably. The physician interested in an excellent concise summary of cerebrovascular disease and its management, would be wise to consult this latter monograph, rather than "Cerebrovascular Disability and the Ageing Brain," which contains little new for generalists or specialists.

ROBERT A. FISHMAN, MD

in memoriam

Butt, Ernest George, Redondo Beach. Died December 13, 1975 in Redondo Beach of malignant melanoma, aged 89. Graduate of University Medical College of Kansas City, 1909. Licensed in California in 1909. Dr. Butt was a member of the Los Angeles County Medical Association.

Cheves, Roswell S., jr., Santa Barbara. Died November 13, 1975, aged 49. Graduate of Columbia University College of Physicians and Surgeons, New York, 1950. Licensed in California in 1955. Dr. Cheves was a member of the Medical Society of Santa Barbara County.

Cord, Robert Ireland, Santa Barbara. Died December 10, 1975 in Santa Barbara of heart disease, aged 58. Graduate of the University of Louisville School of Medicine, 1942. Licensed in California in 1951. Dr. Cord was a member of the Medical Society of Santa Barbara County.

Covey, Herman W., Glendale. Died September 28, 1975 in Glendale of cerebrovascular accident, aged 89. Graduate of McGill University Faculty of Medicine, Toronto, 1907. Licensed in California in 1922. Dr. Covey was a retired member of the Los Angeles County Medical Association.

Dana, Ethel Shepherd (Ethel Shepherd Dana Atkinson), Los Gatos. Was killed December 12, 1975 in a traffic accident on Highway 17, aged 57. Graduate of Cornell University Medical College, New York, 1943. Licensed in California in 1952. Dr. Dana was a member of the Santa Clara County Medical Society.

Dorsey, Philip W., Redlands. Died October 15, 1975 in Mercer Island, Washington, aged 60. Graduate of Syracuse University College of Medicine, 1941. Licensed in California in 1963. Dr. Dorsey was a member of the San Bernardino County Medical Society.

Gallagher, John L., La Jolla. Died November 17, 1975 in La Jolla, aged 77. Graduate of the University of Tennessee College of Medicine, Memphis, 1926. Licensed in California in 1945. Dr. Gallagher was a retired member of the San Diego County Medical Society.

Hartwig, Carl Herman, Alameda. Died December 7, 1975 in Alameda, aged 68. Graduate of Harvard Medical School, Boston, 1932. Licensed in California in 1936. Dr. Hartwig was an associate member of the Alameda-Contra Costa Medical Association.

Jamison, Robert Cecil, Redlands. Died November 26, 1975 in San Jose, aged 59. Graduate of the University of California Medical School, Berkeley-San Francisco, 1942. Licensed in California in 1942. Dr. Jamison was a member of the San Bernardino County Medical Society.

Jones, Orion Chester, Visalia. Died December 15, 1975 of acute myocardial infarction, aged 83. Graduate of the University of Illinois College of Medicine, Chicago, 1918. Licensed in California in 1919. Dr. Jones was a retired member of the Tulare County Medical Society.

McCandliss, Charles H., Los Angeles. Died October 1, 1975 in Inglewood of leukemia, aged 71. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1932. Licensed in California in 1932. Dr. McCandliss was a member of the Los Angeles County Medical Association.

Meens, David F., Hemet. Died April 28, 1975 of biliary adenocarcinoma with metastases, aged 58. Graduate of the University of Southern California School of Medicine, Los Angeles, 1943. Licensed in California in 1943. Dr. Meens was a member of the Riverside County Medical Association.

Nebeker, Don Paul, Arcadia. Died in late November, 1975 in Big Bear of injuries received in plane crash, aged 70. Graduate of Northwestern University Medical School, Chicago, 1936. Licensed in California in 1937. Dr. Nebeker was a member of the Los Angeles County Medical Association.

Papageorges, Nicholas P., jr., Long Beach. Died November 25, 1975 in Long Beach of cerebrovascular accident, aged 52. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1955. Licensed in California in 1956. MD degree from California College of Medicine, 1962. Dr. Papageorges was a member of the Los Angeles County Medical Association.

Pattison, Arthur Colman, Pasadena. Died May 21, 1975 of azotemia due to leukemia, aged 68. Graduate of the State University of Iowa College of Medicine, Iowa City, 1930. Licensed in California in 1937. Dr. Pattison was a retired member of the Los Angeles County Medical Association.

Pillsbury, Philip L., San Francisco. Died December 5, 1975 in San Francisco, aged 61. Graduate of Harvard Medical School, Boston, 1940. Licensed in California in 1946. Dr. Pillsbury was a member of the San Francisco Medical Society.

Sailer, Eldor Christ, San Francisco. Died December 24, 1975 in San Francisco of cancer, aged 66. Graduate of Rush Medical College, Chicago, 1935. Licensed in California in 1936. Dr. Sailer was a member of the San Francisco Medical Society.

Steindel, Sam, Los Angeles. Died December 11, 1975 in Los Angeles of heart disease, aged 62. Graduate of the University of California Medical School, Berkeley-San Francisco, 1941. Licensed in California in 1941. Dr. Steindel was a member of the Los Angeles County Medical Association.

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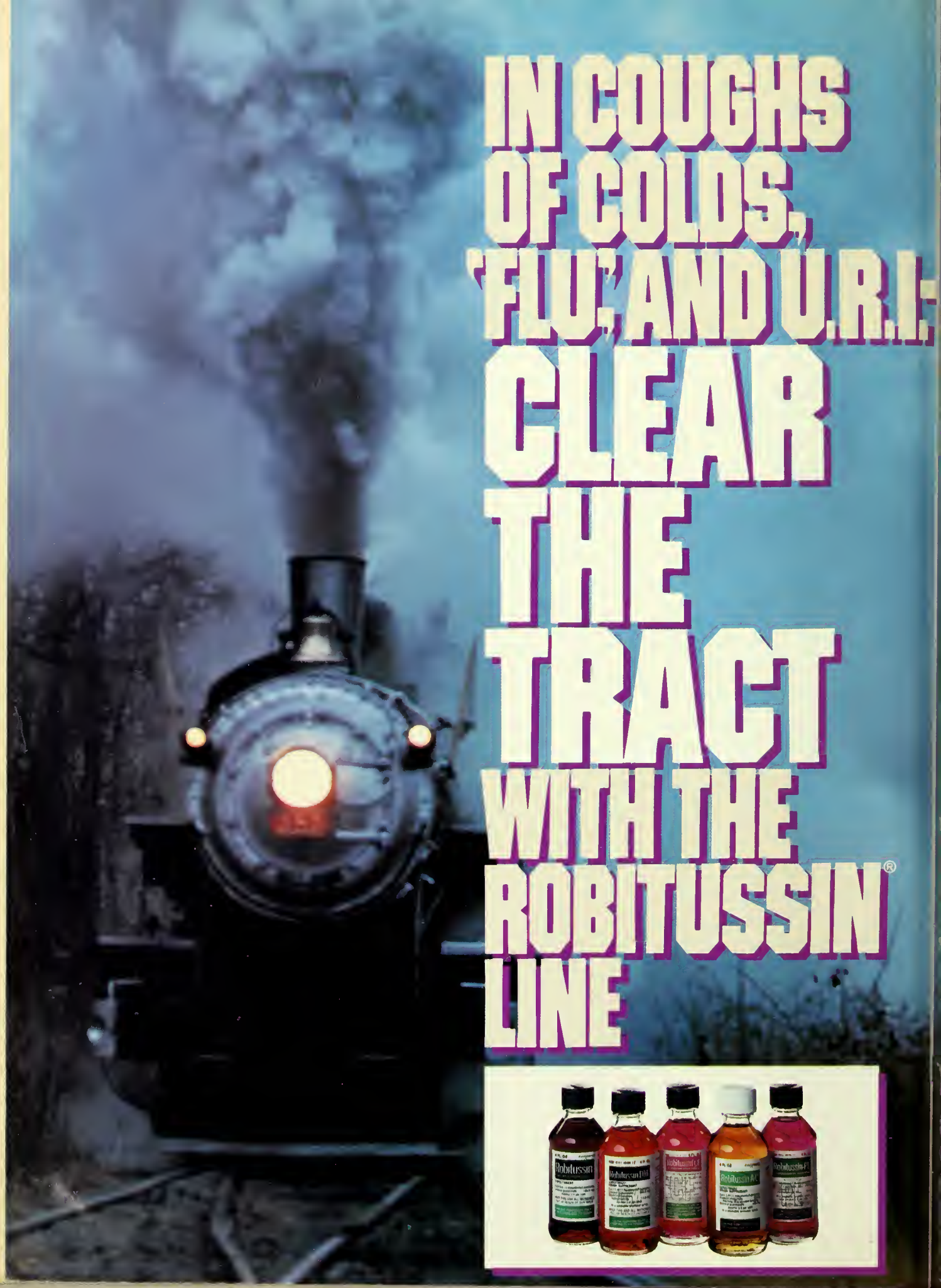
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The William Mason (1856)

(Continued from Page 16)

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IMMEDIATE OPENING for full-time physician to join Medical Division of large international petrochemical company in Midwest. Board certified in internal medicine, or would consider board qualified. Salary negotiable, plus numerous company benefits. Anyone interested should respond to Phillips Petroleum Company, Medical Director, B 57 Adams Building, Bartlesville, OK 74004.

SENIOR PHYSICIAN at the Nevada State Prison, Carson City: Performs professional medical duties and supervises medical technicians. Must possess or be eligible for a license or permit to practice medicine in the State of Nevada. Salary: up to $35,331 for applicants who are Board-eligible in a medical specialty, and up to $32,098 for one year internship in an approved hospital plus three years experience in the practice of medicine. Contact Donna Green in the Nevada State Personnel Division, Carson City, Nevada 89701.

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THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: For a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education, please write to the above address.

ALCOHOLISM AND DRUG ABUSE

February 21-22—**Psychiatric Techniques in the Treatment of Drug Abuse and Alcoholism.** UCLA. Saturday-Sunday.

April 3—**Poly Drug Abuse.** USC. Saturday.

May 21-23—**Alcoholism and Drug Abuse.** UCSF. Friday-Sunday.

May 27-29—**National Conference on Radiation Oncology.** American Cancer Society at Hilton Hotel, San Francisco. Thursday-Saturday. Contact: S. L. Arje, MD, ACS, 219 E. 42nd St., New York 10017.

CANCER

February 27—**Breast Cancer.** UCSF at Childrens Hospital and Medical Center, San Francisco. Friday.

February 27—**Current Cancer Therapy Concepts and the Animal Patient Role.** Kern County Unit, American Cancer Society. Friday. 8 hrs. $25. Contact: Elizabeth Bell, Exec. Dir., Kern County Unit, ACS, 238 18th St., Suite 10, Bakersfield 93301. (805) 325-5117.

March 4-7—**Seminar on Modern Concepts in Oncology—4th Annual.** UCLA at Beverly Hilton Hotel, Beverly Hills. Thursday-Sunday.

March 26—**Colo-Rectal Carcinoma.** California Hospital Medical Center, Los Angeles. Friday. 10 hrs. $15. Contact: Kenneth L. Senter, MD, Dir., Med. Ed., CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411.

April 3—**Oncology Update 1976.** Alta Bates Hospital, Berkeley. Saturday. 8 hrs. $20. Contact: Norman Cohen, MD or Harry Newman, MD, Alta Bates Hospital, No. 1 Colby Plaza, Berkeley 94705. (415) 845-7110.

MEDICINE

February 16-20—**Topics in Internal Medicine. UCSD** at Town and Country Hotel, San Diego. Monday-Friday.

February 17—**Seminars in Nephrology.** USC. Tuesday, 7-10 p.m. First of six seminars; one every three months; through February 1977.

February 25-27—**Advances in the Diagnosis and Treatment of Pulmonary Disease.** California Thoracic Society at Sheraton-Harbor Island Hotel, San Diego. Wednesday-Friday. 20 hrs. $135 for members; $160, non-members. Contact: Ms. Elma Plappert, Exec. Sec., CTS, 424 Pendleton Way, Oakland 94621. (415) 638-5864.

February 26-27—**Dermatologic Therapy for the Practicing Physician.** UCSF at St. Francis Hotel, San Francisco. Thursday-Friday.

February 26-28—**Pediatric Hematology.** See Pediatrics, February 26-28.

February 27-28—**Pulmonary Artery Catheterization.** PMC. Fri.-Sat.

March 1-5—**Electrophysiology.** USC at Erawan Garden Hotel, Palm Springs. Monday-Friday.

March 4-6—**Cardiology '76—Practical Aspects of Cardiac Care.** American Heart Assn.-Golden Empire Chapter at Sahara Tahoe Hotel, Lake Tahoe. Thursday-Saturday. Contact: AHA-Golden Empire Chapter, P.O. Box 16011, Sacramento 95816. (916) 444-8650.

March 4-7—**American College of Physicians-Southern California Regional Meeting.** Riviera Hotel, Palm Springs. Thursday-Sunday. Contact: Varner J. Johns, Jr., MD, FACP, Loma Linda Medical Center, Loma Linda 92354.

March 5—**Diabetes—3rd Annual Program.** UCD at Red Lion Inn, Sacramento. Friday.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

March 11-13—**Cardiovascular Disease—1976: Practical Diagnosis and Management.** American College of Cardiology at La Costa Resort Hotel, San Diego. Thursday-Saturday. Contact: ACC, 9650 Rockville Pike, Bethesda, MD 20014.

March 12-13—**Southwestern Professional Diabetes Symposium—4th Annual.** American Diabetes Assn., Southern Calif. Affiliate, Inc., at Century Plaza Hotel, Los Angeles. Friday-Saturday. Contact: Donald E. McMillan, MD, Sansum Medical Research Foundation, P.O. Drawer LL, Santa Barbara 93102. (805) 963-4358.

March 20—**Echocardiography Workshop.** PMC at Miyako Hotel, San Francisco. Saturday.

March 22-April 2—**Intensive Review of Internal Medicine—24th Annual.** USC. Two weeks.

March 24-26—**Hepato-Biliary Disease.** PMC at Mark Hopkins Hotel, San Francisco. Wednesday-Friday.

March 26-27—**Pulmonary Artery Catheterization.** PMC. Friday-Saturday.

March 26-27—**New Perspectives in Exercise Stress Testing.** American College of Cardiology; Memorial Hospital Medical Center, Long Beach; UCI at Center for Health Education, Memorial Hospital, Long Beach. Friday-Saturday. Contact: ACC, 9650 Rockville Pike, Bethesda, MD 20014.

March 30-April 2—**Consultant's Course in Dermatology.** UCSF. Tuesday-Friday.

April 1-2—**Current Problems in Intensive Care: Pulmonary Edema.** UCSF at St. Francis Hotel, San Francisco. Thursday-Friday.

April 1-2—**Core Curriculum: Cardiovascular Physiology: Clinical Implications of Newer Concepts and Measurements.** American College of Cardiology at Cedars-Sinai Medical Center, Los Angeles. Thursday-Friday. Contact: ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

April 1-3—**Advances in Cardiology.** Foundation for Cardiovascular Research and Hospital of the Good Samaritan at Balboa Bay Club, Newport Beach. Thursday-Saturday. Contact: Foundation for Cardiovascular Research, 39 Congress St., Pasadena 91105.

April 2-3—**Recent Advances in Endocrinology.** USC at Erawan Gardens, Palm Springs. Friday-Saturday.

April 3—**Gastroenterology Symposium.** Central Calif. Committee for Gastroenterology at Fresno Community Hospital. Saturday. $25. Contact: Mr. Remi Barron, Central San Joaquin Valley Area Health Education Center, 5110 E. Clinton Way, Suite 115, Fresno 93727. (209) 252-2851.

April 5-14—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe. 10 days. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

April 6-July 13—**Intensive Review of Recent Advances in Internal Medicine.** UCLA. Tuesdays, 7-10 p.m. 57 hrs. $135.

April 11-16—**American Association of Immunologists.** Royal Hotel, Anaheim. Sunday-Friday. Contact: H. Metzger, MD, Sec.-Treas., AAI, 9650 Rockville Pike, Bethesda, Md. 20014.

April 26-30—**Advances in Internal Medicine.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday.

April 30—**Flexible Bronchofibroscopy II.** PMC. Friday.

May 6-8—**Arrhythmias: Basic and Clinical Aspects.** PMC at Golden Gateway Holiday Inn, San Francisco. Thursday-Saturday.

May 7-8—**Coagulation Update 1976.** UCSF. Friday-Saturday.

May 21—**Diagnosis and Treatment of Hypertension.** PMC. Friday.

OBSTETRICS AND GYNECOLOGY

February 18-20—**Neonatal Medicine.** USC. Wednesday-Friday.

February 24-26—**Ob Infectious Diseases.** USC. Tuesday-Thursday.

March 1-3—**New Vistas for Perinatal Critical Care.** USC. Monday-Wednesday.

March 5-7—**Obstetric Anesthesia Conference—Part I.** L.A. Obstetrical & Gynecological Society at Sheraton Airport Hotel, Los Angeles. Friday-Sunday. Contact: Perinatal Anesthesia, P.O. Box 54508, Los Angeles 90054. (213) 226-3311.

March 8-11—**Obstetric Anesthesia Conference—Part II.** L.A. Obstetrical and Gynecological Society at Sheraton-Maui Hotel, Maui, Hawaii. Monday-Thursday. Contact: Perinatal Anesthesia, P.O. Box 54508, Los Angeles 90054. (213) 226-3311.

March 13—**Regional Perinatal Care Conference.** CMA at Hollywood Presbyterian Hospital, Hollywood. Saturday. Contact: George Feiler, CMA.

April 2-3—**Obstetrics and Gynecology: Workshop in Intrapartum Fetal Monitoring.** UCSF. Friday-Saturday.

May 15-16—**Gyn-Urology.** USC at Biltmore Hotel, Santa Barbara. Saturday-Sunday.

PEDIATRICS

February 18—**The Pediatrician's Obligation in the Atherosclerosis Epidemic.** American Heart Assn., Greater L.A. Affiliate, and L.A. Pediatric Society at Hyatt Regency Hotel, Los Angeles. Wednesday. Contact: Nancy Brown, AHA, Greater L.A. Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

February 21—**The Teenager's Doctor—A Key to Understanding Youth.** American Academy of Pediatrics, No. Calif. Chapter, at Children's Hospital, San Francisco. Saturday. 6 hrs. $25. Contact: Richard C. Brown, MD, Dept. of Pediatrics, Children's Hospital, 3700 California St., San Francisco 94119. (415) 387-8700.

February 26-28—**Pediatric Hematology—Annual Winter Meeting.** Children's Hospital Medical Center of Northern Calif. at Sahara Tahoe Hotel, South Lake Tahoe. Thursday-Saturday. Contact: Inetta Carty Calori, CHMC, 51st & Grove Sts., Oakland 94609.

March 19-21—**Combined Southern California Pediatric Postgraduate Meeting: Clinical Pediatrics.** Calif. Chapter 2, District IX, American Academy of Pediatrics, at Riviera Hotel, Palm Springs. Friday-Sunday. Contact: Eve Black, Exec. Sec., P.O. Box 2134, Inglewood 90305.

March 20—**Pediatric Subspecialty Problems in Office Practice.** Mt. Zion Hospital & Medical Center, San Francisco. Saturday. $40. 6 hrs. Contact: Continuing Education, Mt. Zion Hospital & Medical Center, P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2401.

March 26-27—**Pediatric Topics 1976: Neonatology and Pediatric Cardiology.** UCD and Sacramento Pediatric Society at Mansion Inn, Sacramento. Friday-Saturday. Contact: UCD.

April 23-24—**Pediatric Ophthalmology.** See Surgery, April 23-24.

April 24-May 1—**Pediatric Review.** USC at Maui Surf, Hawaii. One week.

May 3-7—**Pediatric Review—6th Annual.** USC. Monday-Friday.

May 8-9—**Learning Disabilities in Children.** UCLA. Saturday-Sunday.

May 13-15—**Annual Pediatric Course.** UCSF. Thursday-Saturday.

May 21-23—**American Academy of Pediatrics, California Chapter I, District IX.** Ahwahnee Hotel, Yosemite. Friday-Sunday. Contact: Melvin H. Schwartz, MD, 2219 Santa Clara Ave., Alameda 94501.

May 23-26—**Recent Advances in Pediatric Neurology.** UCLA at Ahwahnee Hotel, Yosemite. Sunday-Wednesday.

PSYCHIATRY

February 16-20—**Treating Distressed Couples: The Masters and Johnson Method.** Center for Counseling Skills, Kentfield, at Santa Barbara. Monday-Friday. Contact: Mrs. Tina Coffman, Extension Office, UCSB, Santa Barbara 93106.

February 21-22—**Introduction to Clinical Hypnosis and Behavior Modification.** UCLA at Americana Hotel, Los Angeles. Saturday-Sunday.

February 21-22—**Psychiatric Techniques in the Treatment of Drug Abuse and Alcoholism.** UCLA. Saturday-Sunday.

February 27-29—**Current Therapy for Marital-Sexual Dysfunction.** The Center for Counseling Skills, Kentfield, at Palo Alto. Friday-Sunday. Contact: Center for Creativity and Growth, Suite 154, 770 Welch Rd., Palo Alto 94304. (415) 327-4477.

March 5-7—**Current Therapy for Marital-Sexual Dysfunction.** Center for Counseling Skills, Kentfield, at Palo Alto. Friday-Sunday. Contact: Center for Creativity and Growth, Suite 154, 770 Welch Rd., Palo Alto 94304. (415) 327-4477.

March 6-7—**Biofeedback Workshop.** UC Extension, Santa Cruz; Gladman Memorial Hospital, Oakland, at Terman Jr. High School, Palo Alto. Saturday-Sunday. 6 hrs. Contact: Darla Chadima, Coordinator, Programs for Physicians, UC Extension, Santa Cruz 95064. (408) 429-2971.

March 13-14—**Advanced Workshop in Hypnosis and Behavior Modification.** UCLA at Marina City Club, Marina Del Rey. Saturday-Sunday.

March 18—**The Compromised Psychophysiologic State or "Why Can't You Make Me Well?"** See Of Interest To All, March 18.

April 11-15—**Psychiatric Update—3rd Annual Seminar.** UCLA at Riviera Hotel, Palm Springs. Sunday-Thursday.

May 8-9—**Learning Disabilities in Children.** See Pediatrics, May 8-9.

May 16-19—**Biofeedback—3rd Annual Program.** UCLA at Ahwahnee Hotel, Yosemite. Sunday-Wednesday.

RADIOLOGY AND PATHOLOGY

March 13-14—**Diagnostic Nuclear Imaging.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

March 15-19—**Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday.

March 20-21—**Ultra Sound, A Practical Course.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

March 21-25—**Cardiac Radiology Refresher Course.** North American Society for Cardiac Radiology at Sir Francis Drake Hotel, San Francisco. Sunday-Thursday. Contact: Erik Carlsson, MD, Dept. of Radiology, UCSF.

April 11-16—**American Society for Experimental Pathology.** Anaheim. Sunday-Friday. Contact: Am. Soc. for Experimental Pathology, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-7130.

May 5-8—**Nuclear Medicine—6th Annual Spring Symposium.** Sierra Valley Nuclear Medicine Assn.; No. Calif. Chapter, Society of Nuclear Medicine, at Convention Center, Lake Tahoe. Wednesday-Saturday. Contact: Darleen Nelson, Nuclear Medicine Dept., Mercy San Juan Hospital, 6501 Coyle Ave., Carmichael 95608.

SURGERY AND ANESTHESIOLOGY

March 5—**Strabismus Surgery Workshop.** Jules Stein Eye Institute, Los Angeles. Friday. Contact: Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles.

March 5-7—**Obstetric Anesthesia Conference, Part I.** See Obstetrics and Gynecology, March 5-7.

March 6-7—**American Society of Anesthesiologists Workshop.** Sheraton-Harbor Island Hotel, San Diego. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, Ill. 60068.

March 8-11—**Obstetric Anesthesia Conference, Part II.** See Obstetrics and Gynecology, March 8-11.

March 9-13—**Seminar on Controversial Areas in Surgery—13th Annual.** UCLA at Canyon Hotel, Palm Springs. Tuesday-Saturday.

March 11-12—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

March 12-13—**Hand Injuries and Infections.** PMC. Friday-Saturday.

March 13-17—**Multidiscipline Symposium and Workshop on Management of Trauma—3rd Annual.** UCLA at Canyon Hotel, Palm Springs. Saturday-Wednesday.

March 14-26—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. 100 hrs. $1,200 for otolaryngologists; $900, residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

March 17-21—**Symposium on Vascular Surgery—4th Annual.** UCLA at Canyon Hotel, Palm Springs. Wednesday-Sunday.

March 18-19—**Diseases of the Urinary Tract—4th Annual Symposium.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday.

March 22-26—**Anesthesiology—1976.** Anesthesiology Education Foundation and Calif. Society of Anesthesiologists at Mammoth Lakes. Monday-Friday. Contact: Ronald L. Katz, MD, Dept. of Anesthesiology, UCLA.

March 22-26—**Trauma and Surgical Emergencies.** STAN. Monday-Friday.

March 27-30—**Jaws: Reconstructive Surgery of Developmental and Acquired Deformities.** UCLA. Saturday-Tuesday.

April 2—**Corneal Surgery Workshop.** Jules Stein Eye Institute, Los Angeles. Friday. Contact: Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles.

April 7-10—**California Thoracic Society—Annual Scientific Sessions.** Rickey's Hyatt House, Palo Alto. Wednesday-Saturday. Contact: Ms. Elma Plappert, Exec. Sec., CTS, 424 Pendleton Way, Oakland 94621. (415) 638-5864.

April 8-9—**Ophthalmic Skills.** PMC. Thursday-Friday.

April 8-9—**Office Orthopedics.** USC. Thursday-Friday.

April 9-10—**Phacoemulsification Conference.** St. Mary's Hospital and Medical Center, San Francisco. Friday-Saturday. Contact: J. Albert Sarrai, MD, 450 Sutter St., San Francisco. (415) 397-1500.

April 22-23—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

April 22-24—**General Surgery—Annual Course.** UCSF at Hilton Hotel, San Francisco. Thursday-Saturday.

April 23-24—**Pediatric Ophthalmology—A Current Review—7th Annual Jules Stein Lecture and Postgraduate Seminar.** Jules Stein Eye Institute at Beverly Hilton Hotel, Los Angeles. Friday-Saturday. Contact: Jules Stein Eye Institute, UCLA.

April 23-25—**American Association for Thoracic Surgery.** Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Mr. W. T. Maloney, Exec. Sec., 6 Beacon St., Suite 620, Boston, Mass. 02108. (617) 227-0760.

May 1-8—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

May 4-7—**Samuel Higby Camp—Orthopedic Surgery.** UCSF. Tuesday-Friday.

May 16-28—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. 100 hrs. $1,200 for otolaryngologists; $900 for residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

May 20-21—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

May 20-22—**Neurosurgery—6th Annual Postgraduate Course.** UCSF at St. Francis Hotel, San Francisco. Thursday-Saturday.

May 23-26—**Recent Advances in Pediatric Neurology.** See Pediatrics, May 23-26.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

February 15-19—**Sports Medicine for Primary Physicians.** Univ. of Hawaii School of Medicine at North Shore of Oahu, Hawaii. $200. Sunday-Thursday. Contact: Richard H. Strauss, MD, Univ. of Hawaii Conference Ctr., 2500 Dole St., Honolulu 96822.

February 16-20—**Treating Distressed Couples: The Masters and Johnson Method.** See Psychiatry, February 16-20.

February 20—**Total Parenteral Nutrition Workshop.** UCD at Red Lion Inn, Sacramento. Friday.

February 27-29—**Current Therapy for Marital-Sexual Dysfunction.** See Psychiatry, February 27-29.

February 28-29—**Infectious Disease and Pulmonary Disease for Family Practitioners.** UCLA. Saturday-Sunday.

March 1-5—**Basic Science for Clinicians.** STAN. Monday-Friday.

March 5-7—**Current Therapy for Marital-Sexual Dysfunction.** See Psychiatry, March 5-7.

March 7-11—**LLU Alumni Postgraduate Convention.** Sunday-Thursday.

March 7-12—**Emergency Medical Care Review—Part II.** UCD at Hyatt Lake Tahoe Hotel, Incline Village. Sunday-Friday.

March 12—**Diagnosis and Treatment of Hypertension.** See Medicine, March 12.

March 13-17—**Multidiscipline Symposium and Workshop on Management of Trauma.** See Surgery, March 13-17.

March 18—**The Compromised Psychophysiologic State or "Why Can't You Make Me Well?"** Eden Hospital at Willow Park Country Club, Castro Valley. Thursday. 7 hrs. $35. Contact: Ms. Eleanor Sample, Eden Hospital, 20103 Lake Chabot Rd., Castro Valley. (415) 537-1234, ext. 211.

March 19—**Office Management of Parkinsonism.** PMC at Miyako Hotel, San Francisco. Friday.

March 21-23—**Sports Injury Clinic.** CMA, Medical Education Foundation of Santa Barbara County and UCLA at Lakeland Village, Lake Tahoe. Sunday-Tuesday. Contact: Richard Manley, CMA.

March 22-26—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday.

March 29-April 2—**Basic and Applied Pharmacology.** STAN. Monday-Friday.

April 1-2—**Current Problems in Intensive Care: Pulmonary Edema.** See Medicine, April 1-2.

April 8-10—**Otolaryngology for the GP.** UCSF. Thursday-Saturday.

April 23-24—**West Coast Counties Postgraduate Institute.** CMA at Quail Lodge, Carmel Valley. 14 hrs. $60 for CMA members; $90, non-members. Friday-Saturday. Contact: Richard Manley, CMA.

April 24—**5th Annual Symposium—Fluid and Electrolytes—Management in Clinical Practice.** South Coast Community Hospital, South Laguna. Saturday. 8 hrs. $25. Contact: Eugene B. Levin, MD, Dir. of Med. Ed., SCCH, 31872 Coast Highway, South Laguna 92677. (714) 499-1311, ext. 136-137.

April 26-May 1—**Emergency Medicine.** USC at Kauai Surf, Kauai, Hawaii. Monday-Saturday.

April 26-May 1—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Saturday.

April 29-May 1—**Psychosocial Care of Dying Patient—Doctor:Patient Relationship.** UCSF at St. Francis Hotel, San Francisco. Thursday-Saturday.

April 29-May 2—**Medicine and Related Techniques in the Treatment of Musculoskeletal Pain.** USC. Thursday-Sunday.

May 10-15—**Diving Medicine.** UCSF at VA Hospital, Fresno. Monday-Saturday.

May 10-21—**Family Practice—Intensive Review.** USC. Two weeks.

May 14-15—**San Joaquin Valley Counties Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Friday-Saturday. $60 for CMA members; $90, non-members. Contact: Richard Manley, CMA.

May 17-21—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

May 21—**Diagnosis and Treatment of Hypertension.** See Medicine, May 21.

May 29-30—**Opportunistic Fungus Diseases.** UCSF. Saturday-Sunday.

Audio-Digest Foundation. A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: Family Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $90 per year. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90057. (213) 483-3451.

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Family Practice Center, 3181 S.W. Sam Jackson Park Road, Portland 97201:

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School.

FAMILY PRACTICE

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Family Practice Center, University of Oregon Medical School, Portland. Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

February 16-20—**Seventh Annual General and Family Practice Review.** Sheraton Motor Inn, Portland. Contact: William Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 S.W. Sam Jackson Park Road, Portland, OR 97201.

INTERNAL MEDICINE

May 20-22—**Oregon Society of Internal Medicine Annual Meeting.** Sunriver Lodge, Sunriver, Oregon. Contact: Donald R. Olson, MD, Oregon Society of Internal Medicine, 2164 S.W. Park Place, Portland 97205.

PHYSICAL MEDICINE AND REHABILITATION

April 30-May 1—**Northwest Association of Physical Medicine and Rehabilitation Annual Meeting.** Jantzen Beach Thunderbird, Portland. Contact: John E. Stanwood, MD, Emanuel Hospital, 2801 N. Gantenbein, Emanuel East, Room 370, Portland 97227.

SURGERY

April 2-3—**American College of Foot Surgeons, Western Division.** Portland Hilton Hotel, Portland. Contact: Robert L. Rutherford, D.P.M., 400 - 40th Street, Oakland, California 94609

OF INTEREST TO ALL PHYSICIANS

February 19-21—**14th Annual Chest Disease Conference.** Salishan Lodge, Gleneden Beach, Oregon 97388. Contact: Oregon Thoracic Society, 830 Medical Arts Building, Portland 97205.

March 30-31—**The Elderly and Their Health Care.** Good Samaritan Hospital, Portland. Contact: S. Spence Meighan, MD, Good Samaritan Hospital and Medical Center, 1015 N.W. 22nd, Portland 97210.

WASHINGTON, MONTANA, ALASKA and IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

February 27-28—**Comprehensive Care of the Burned Patient.** Friday-Saturday. Washington Plaza Hotel, Seattle. 11 hrs. Physicians, $125; nurses, $65; therapists and residents, $60. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 4-6—**Symposium on Cancer: Concepts, Care and Ethics.** Swedish Hospital Medical Center, Seattle. Limited to 200. $15. Contact: Office of Medical Education, The Swedish Hospital Medical Center, 747 Summit Ave., Seattle 98104. (206) 292-2266.

March 5-6—**Recent Advances in Renal Disease—27th Annual Spokane Society of Internal Medicine Scientific Session.** Friday-Saturday. Sheraton Hotel, Spokane, WA. AAFP credit approved. Contact: Thomas A. Marr, MD, 312 W. 8th, Spokane, WA 99204. (509) 838-2531.

March 9-10—**Treating the Untreatable—Univ. of Washington School of Medicine's Western Washington Circuit Course.** Port Angeles, 9; Everett, 10. 4 hrs. Physicians, $25; others, $10. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 12-13—**Orthopedic Disease: A Practical Approach to Clinical Management.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

March 15-19—**Emergency Medicine Institute.** Monday-Friday. Univ. of Wash. Sch. of Med., Seattle. Limited to 16. 38 hrs. $275. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 18-19—**American Society of Clinical Pharmacology and Therapeutics.** Thursday-Friday. Washington Plaza Hotel, Seattle. Contact: E. H. Funk, MD, 1718 Gallagher Rd., Norristown, PA 19401. (215) 277-3831.

March 18-19—**Evaluation and Management of Behavior Problems in the Elderly.** Thursday-Friday. Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 22-26—**Advances in Family Practice.** Monday-Friday. Child Development and Mental Retardation Center, Univ. of Wash., Seattle. Limited to 90. Approximately 35 hrs. $100. Contact Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 25-26—**Immediate Care of the Sick and Injured.** Thursday-Friday. Univ. of Wash. Sch. of Med. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 1-2—**Medical-Dental Management of Oro-facial Pain.** Thursday-Friday. University Tower Hotel, Seattle. Limited to 60. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 1-2—**Clinical Pharmacology for the Practicing Physician.** Thursday-Friday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

April 9—**Gastroenterology for Non-Gastroenterologists.** Friday. Seattle. Limited to 150. Location, hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 12-16—**Emergency Medicine Institute.** Monday-Friday. Univ. of Wash. Sch. of Med., Seattle. Limited to 16. 38 hrs. $275. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 23—**Current Concepts in Nutrition.** Friday. University Tower Hotel, Seattle. Hours and fees to be determined. Contact Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 24—**Current Concepts in Nutrition.** Saturday. Spokane. Location, hours and fees to be determined. Contact Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 22-23—**Respiratory Care Conference.** Thursday-Friday. Seattle. Location, hours and fees to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 28-30—**Medicine and Law.** Wednesday-Friday. Seattle. Location, hours and fees to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 6-7—**Surgical Therapeutics.** Thursday-Friday. Washington Plaza Hotel, Seattle. Limited to 200. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 7-8—**Regional Block Anesthesia.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

May 12-14—**Advances in Internal Medicine.** Wednesday-Friday. Olympic Hotel, Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 14-23—**Tax, Estate and Financial Planning.** Friday-Monday. Aboard the SS Rotterdam; 7-day cruise to Nassau and Bermuda. 25 hrs. $200. Contact: Richard L. Reimer, Asst. Dir. CME, T87 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 16-20—**Pacific Coast Oto-Ophthalmological Society.** Sunday-Wednesday. Washington Plaza Hotel, Seattle. Contact: M. F. W. Smith, MD, Ear Medical Clinic of Santa Clara Valley, 2120 Forest Ave., Suite 2, San Jose, CA 95128.

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May 20—**Endocrinology.** Thursday. Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 20-21—**Pediatric Care for General Practitioners.** Thursday-Friday. Children's Orthopaedic Hospital and Medical Center, Seattle. Hours and fee to be determined. Contact: William O. Robertson, MD, Dir. Med. Ed., Children's Orthopaedic Hospital and Medical Center, 4800 Sand Point Way NE, Seattle 98105. (206) 634-5072.

May 21-22—**Sports Medicine—1976.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

May 24-28—**Treating the Untreatable—Univ. of Washington School of Medicine's Montana Circuit Course.** Great Falls, 24th; Billings, 25th; Bozeman, 26th; Missoula, 27th; Whitefish/Kalispell, 28th. 4 hrs. Physicians, $25; others, $10. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

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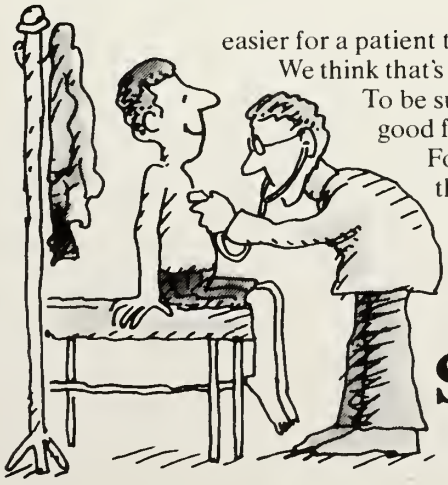

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Indications: Acute, recurrent or chronic nonobstructed urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms. ***Note:* Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides, especially in chronic or recurrent urinary tract infections.** Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Sulfonamide hypersensitivity; pregnancy at term and during nursing period; infants less than two months of age.

Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

Dosage: *Systemic sulfonamides are contraindicated in infants under 2 months of age* (except adjunctively with pyrimethamine in congenital toxoplasmosis).

Usual adult dosage: 2 Gm (4 tabs or teasp.) initially, then 1 Gm *b.i.d.* or *t.i.d.* depending on severity of infection.

Usual child's dosage: 0.5 Gm (1 tab or teasp.)/20 lbs of body weight initially, then 0.25 Gm/20 lbs *b.i.d.* Maximum dose should not exceed 75 mg/kg/24 hrs.

Supplied: Tablets, 0.5 Gm sulfamethoxazole; Suspension, 0.5 Gm sulfamethoxazole/teaspoonful.

ROCHE

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Bacterial proliferation in the urine is a function of time and retention, as the chart below indicates. Because each 1-Gm dose provides up to 12 hours' antibacterial activity, Gantanol protects the patient during the hours of sleep, when urinary retention favors bacterial buildup in the bladder. Counts of susceptible *E. coli* are usually reduced from 10^5/ml to sterile urine within 48 hours.

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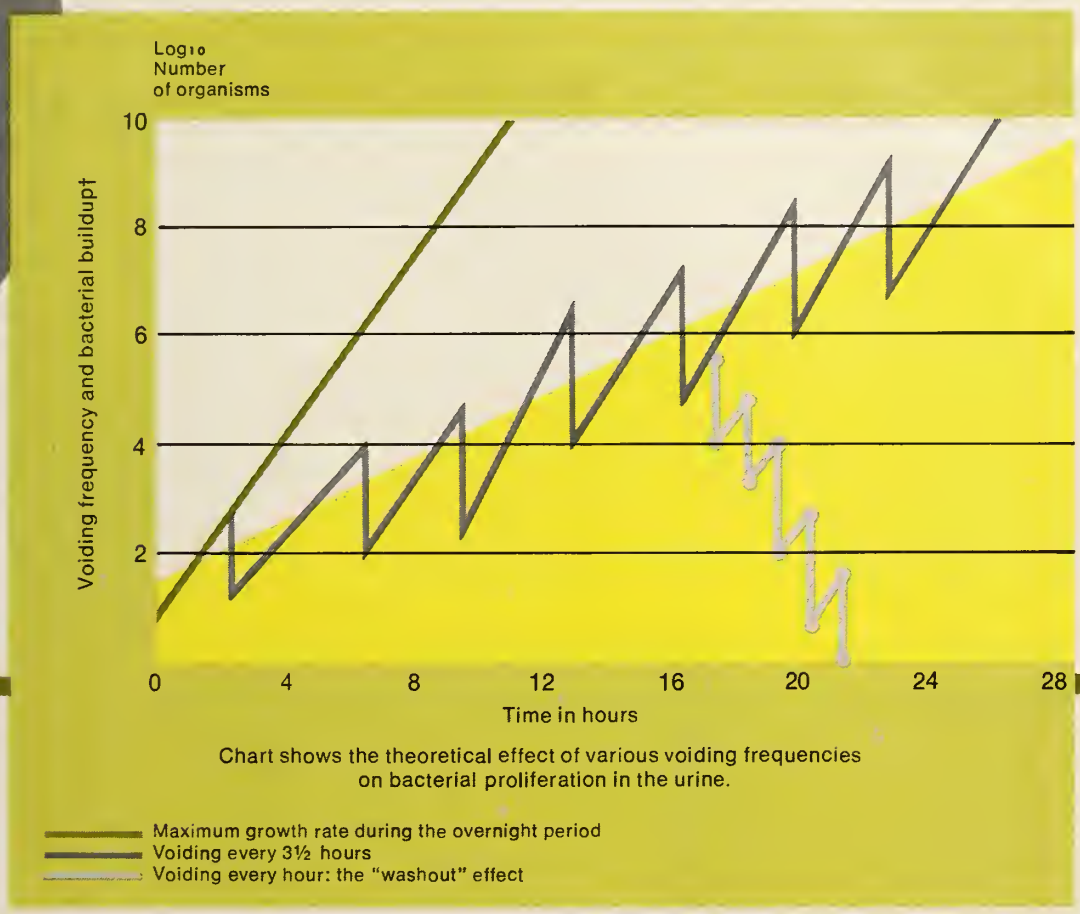

Chart shows the theoretical effect of various voiding frequencies on bacterial proliferation in the urine.

†Adapted from O'Grady F, Cattell WR: *Brit J Urol 38*:156, 1966

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

BACTERIOLOGY AND IMMUNITY FOR NURSES—Fourth Edition—Ronald Hare, MD, Emeritus Professor of Bacteriology, University of London, and formerly Honorary Consulting Bacteriologist to St. Thomas's Hospital; and E. Mary Cooke, B Sc, MD, MRCPatr, Professor of Clinical Microbiology, University of Leeds, and Honorary Consultant in Clinical Microbiology to the Leeds Area Health Authority (Teaching) Western District. Churchill Livingstone, Medical Division of Longman, Inc., 72 Fifth Avenue, New York City (10011), 1975. 175 pages, $9.50.

BIOCHEMISTRY—Lubert Stryer, Yale University. W. H. Freeman and Company, 660 Market Street, San Francisco (94104), 1975. 877 pages, with 626 illustrations, $19.95.

THE CENTENARIANS OF THE ANDES—David Davies—Anchor Press/Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1975. 150 pages, $6.95.

COMPLEMENT: MECHANISMS AND FUNCTIONS—Abraham G. Osler, PhD, The Public Health Research Institute of the City of New York and New York University School of Medicine—One of the Prentice-Hall Foundations of Immunology Series—Editors: Abraham Osler and Leon Weiss. Prentice-Hall, Inc., Englewood Cliffs, NJ (07632), 1976. 193 pages, $18.95.

CURRENT MEDICAL DIAGNOSIS & TREATMENT 1976—Marcus A. Krupp, MD, Clinical Professor of Medicine, Stanford University School of Medicine, Director of Research, Palo Alto Medical Research Foundation, Director of Laboratories, Palo Alto Medical Clinic; Milton J. Chatton, MD, Clinical Professor of Medicine, Stanford Unversity School of Medicine, Senior Attending Physician, Santa Clara Valley Medical Center, San Jose, Research Associate, Palo Alto Medical Research Foundation; and Associate Authors. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1976. 1062 pages, $14.00.

FOR YOURSELF: The Fulfillment of Human Sexuality—Lonnie Garfield Barbach, PhD, Co-Director, Clinical Training, Human Sexuality Program, University of California, San Francisco. Anchor Press/Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1976. 240 pages, $3.95 (Paperback).

HOW TO HAVE YOUR CAKE & EAT IT TOO!—Norma M. Macrae, RD. Alaska Northwest Publishing Co., Box 4-EEE, Anchorage (99509), 1975. 228 pages, $6.95 (Paperback).

HYPNOSIS IN THE RELIEF OF PAIN—Ernest R. Hilgard, PhD, and Josephine R. Hilgard, MD, PhD, Stanford University. William Kaufmann, Inc., One First Street, Los Altos, CA (94022), 1975. 262 pages, $12.50.

THE INTERNAL AUDITORY MEATUS—Anatomy, Pathology and Surgery—M. Portmann, J. M. Sterkers, R. Charachon and C. H. Chouard; With the assistance of J. P. Pebear, C. Junien-Lavillauroy, J.M. Pelisse and C. Peytral. Churchill Livingstone, Medical Division of Longman, Inc., 72 Fifth Avenue, New York City (10011), 1975. 312 pages, $48.00

LEARNING TO EAT—Behavior Modification for Weight Control—James M. Ferguson, MD, Director, Eating Disorders Clinic, Stanford University School of Medicine. Bull Publishing Co., Box 208, Palo Alto, CA (94302), 1975. Two manuals (one for the therapist and one for the patients), $4.95 each.

MEDICAL RESEARCH—A Statistical and Epidemiological Approach—J. M. England, MB, BS, B Sc, PhD, Member of the Scientific Staff, Medical Research Council's Experimental Haematology Unit, Honorary Lecturer, Department of Haematology, St. Mary's Hospital Medical School, London; Foreword by W.S. Peart, MD, FRCP, FRS, Professor of Medicine, St. Mary's Hospital, London. Churchill Livingstone, Medical Division of Longman, Inc., 72 Fifth Avenue, New York City (10011), 1975. 190 pages, $7.50.

A NURSE'S GUIDE TO ANAESTHETICS, RESUSCITATION AND INTENSIVE CARE—Sixth Edition—The late Walter Norris, MD, FFARCS, Donald Campbell, MB, ChB, FFARCS, DA, Consultant Anaesthetists, Glasgow Royal Infirmary, Honorary Clinical Lecturers in Anaesthetics, University of Glasgow. Foreword by Margaret C.N. Lamb, RGN, Diploma in Nursing (London); Diploma in Education (Chicago). Churchill Livingstone, Medical Division, Longman Inc., 72 Fifth Avenue, New York City (10011), 1976. 160 pages, $7.95.

PEDIATRIC SURGICAL PATHOLOGY—Louis P. Dehner, MD, Associate Professor of Laboratory Medicine and Pathology, University of Minnesota School of Medicine, Minneapolis; With a foreword by John M. Kissane, MD, Professor of Pathology and Pathology in Pediatrics, Washington University School of Medicine, Barnes and Affiliated Hospitals and St. Louis Children's Hospital. The C. V. Mosby Company, Publishers, 3301 Washington Boulevard, St. Louis (63103), 1975. 882 pages, with 823 illustrations, $62.50.

PHILADELPHIA MEDICA—Being a Guide to the City's Historical Places of Health Interest—John Francis Marion. Smith Kline Corporation, 1500 Spring Garden Street, Philadelphia, PA (19101), 1975. 144 pages, 39 photographs in color. Distributed privately to health professionals and institutions by Smith Kline Corporation, distributed to retail book stores by Stackpole Books, Cameron and Kelker Streets, Harrisburg, PA 17105, $4.95.

THE PRACTICE OF CLINICAL IMMUNOLOGY—R. A. Thompson, MB, MRCP, MRC Path, Consultant Immunologist, East Birmingham Hospital. The Williams & Wilkins Company, 428 E. Preston St., Baltimore (21202), 1974. 144 pages, $22.50.

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Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychoses and convulsions. [011375]

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Testing in Humans: Who, Where & When.

the weight of ethical opinion:

Few would disagree that the effectiveness and safety of any therapeutic agent or device must be determined through clinical research.

But now the *practice* of clinical research is under appraisal by Congress, the press and the general public. Who shall administer it? On whom are the products to be tested? Under what circumstances? And how shall results be evaluated and utilized?

The Pharmaceutical Manufacturers Association represents firms that are significantly engaged in the discovery and development of new medicines, medical devices and diagnostic products. Clinical research is essential to their efforts. Consequently, PMA formulated positions which it submitted on July 11, 1975, to the Subcommittee on Health of the Senate Labor and Public Welfare Committee, as its official policy recommendations. Here are the essentials of PMA's current thinking in this vital area.

1. PMA supports the mandate and mission of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and offers to establish a special committee composed of experts of appropriate disciplines familiar with the industry's research methodology to volunteer its service to the Commission.

2. PMA supports the formation of an independent, expert, broadly based and representative panel to assess the current state of drug innovation and the impact upon it of existing laws, regulations and procedures.

3. When FDA proposes regulations, it should prepare and publish in the *Federal Register* a detailed statement assessing the impact of those regulations on drug and device innovation.

4. PMA proposes that an appropriately qualified medical organization be encouraged to undertake a comprehensive study of the optimum roles and responsibilities of the sponsor and physician when company-sponsored clinical research is performed by independent clinical investigators.

5. PMA recognizes that the physician-investigator has, and should have, the ultimate responsibility for deciding the substance and form of the informed consent to be obtained. However, PMA recommends that the sponsor of the experiment aid the investigator in discharging this important responsibility by providing (1) a document detailing the investigator's responsibilities under FDA regulations with regard to patient consent, and (2) a written description of the relevant facts about the investigational item to be studied, in comprehensible lay language.

6. In the case of children, the sponsor must require that informed consent be obtained from a legally appropriate representative of the participant. Voluntary consent of an older child, who may be capable of understanding, in addition to that of a parent, guardian or other legally responsible person, is advisable. Safety of the drug or device shall have been assessed in adult populations prior to use in children.

7. PMA endorses the general principle that, in the case of the mentally infirm, consent should be sought from both an understanding subject and from a parent or guardian, or in their absence, another legally responsible person.

8. Pharmaceutical manufacturers sponsoring investigations in prisons must take all reasonable care to assure that the facilities and personnel used in the conduct of the investigations are suitable for the protection of participants, and for the avoidance of coercion, with a respect for basic humanitarian principles.

9. Sponsors intending to conduct non-therapeutic clinical trials through the participation of employee volunteers should expand the membership and scope of its existing Medical Research Committee, or establish such an internal Medical Research Committee, with responsibility to approve the consent forms of all volunteers, designs, protocols and the scope of the trial. The Committee should also bear responsibility to ensure full compliance with all procedures intended to protect employee volunteers' rights.

10. Where the sponsor obtains medical information or data on individuals, it shall be accorded the same confidential status as provided in codes of ethics governing health care professionals.

11. PMA and its member firms accept responsibility to aid and encourage appropriate follow-up of human subjects who have received investigational products that cause latent toxicity in animals or, during their use in clinical investigation, are found to cause unexpected and serious adverse effects.

12. PMA supports the exploration and development by its member companies of more systematic surveillance procedures for newly marketed products.

13. When a pharmaceutical manufacturer concludes, on the basis of early clinical trials of a basic new agent, that a new drug application is likely to be submitted, a proposed development plan accompanied by a summary of existing data, would be submitted to the FDA. Following a review of this submission, the FDA, and its Advisory Committee where appropriate, would meet with the sponsor to discuss the development plan. No *formal* FDA approval should be required at this stage. Rather, the emphasis should be on identification of potential problems and questions for the sponsor's further study and resolution as the program develops.

The PMA believes that health professionals as well as the public at large should be made aware of these 13 points in its Policy on Clinical Research. For these recommendations envisage constructive, cooperative action by industry, research institutions, the health professions and government to encourage creative and workable responses to issues involved in the clinical investigation of new products.

P·M·A
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12-MAN MULTI-SPECIALTY CLINIC needs ophthalmologist, orthopedic surgeon, otolaryngologist, gynecologist and internist. The present group includes surgeons, internist, urologist, gynecologist and family practitioners. Northeastern Minnesota location with complete hospital facilities. Excellent recreational country, both summer and winter. Complete school system through junior college. Solid and growing economic conditions. No big city problems. Clinic paid profit sharing and pension plans. Malpractice insurance covered by clinic. Beginning salary open and depending upon background and specialty. Ownership participation after one year. Any questions you have will be answered immediately. Please reply—Mesaba Clinic, Hibbing, Minnesota 55746, or call Richard Moyer, MD; (218) 262-3441.

RETIRED, RETIRING GYNECOLOGIST—Some past experience in cytology. Part time, Southern California. A useful, valuable retirement—can you recommend a candidate? Write or phone Pat Kleiman, DSA Medical Group, 6440 Coldwater Canyon Ave., North Hollywood, CA, (213) 877-5336.

(Continued on Page 16)

ASSOCIATE PHYSICIAN INTERNIST

Excellent opportunity in Orange County, California for board eligible or board certified Internist, with or without subspecialty, to establish oneself on an accelerated basis.

Rapidly expanding practice, having a large primary care load, with Cardiology and Cardiac Rehabilitation Orientation.

Presently conducted by 2 Internists in a Medical Corporation which has pension and retirement plans, insurance programs, etc. in place. Ownership participation for associate is intended, with senior physician attaining retirement age in twelve years. Malpractice insurance provided by Corporation. Superior hospital facilities used.

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These dairy foods have several nutrients in common. The principal one is bone-building calcium, which also helps control muscle action and aids in clotting of the blood. Because they all contain calcium, protein and riboflavin, these foods are considered a part of the Milk Group in the U.S. Department of Agriculture's Four Food Groups system.

Some physicians counsel patients in terms of nutrients. Which is easier for them to understand—foods or nutrients?

For attractive, color copies of the Four Food Groups guide for your patients, write: Dairy Council of California, Box 28F, Sacramento, CA 95825.

Dairy Council of California

The Four Food Groups—milk, meat, vegetables and fruits, breads and cereals—a practical guide to good nutrition.

In two separate multicenter studies* of patients with chronic or frequently recurrent urinary tract infections

10 days of Bactrim™ therapy produced better results in maintaining clear cultures than:

10 days of ampicillin therapy

28 days of cephalexin therapy

*Protocols identical except for drug administered and duration of therapy. Protocol details on last page of this advertisement.

Please see summary of product information on last page of this advertisement.

ROCHE

Roche
Research
U.T.I. Study
No. 2

ıe month after therapy ceased, a higher percentage Bactrim-treated patients maintained clear cultures*.

	No. of patients	Therapy	% of clear cultures*
udy o.1	80	10-day Bactrim	71.3%
	76	10-day ampicillin	56.6%
udy No. 2	60	28-day cephalexin	56.7%

on for clear culture: 1000 or fewer organisms/ml of urine.

onth after therapy: 10 days of Bactrim maintained cultures for one month in a larger percentage of ts than either of the other agents. The maintenance ar cultures for one month after therapy has ended articular importance for patients whose problems ronic or recur frequently, for it is during this period elapse or reinfection often occurs.

diately after therapy: Here again, Bactrim results superior. At the end of therapy, 90.4% of 83 patients days of Bactrim had clear cultures, compared with 81.7% of 82 patients on 10 days of ampicillin and 86.6% of 82 patients on 28 days of cephalexin.

Adverse reactions: Side effects in these studies were relatively mild (*e.g.*, nausea, vomiting, rash), but more serious adverse effects can occur with the agents studied. For a complete list of adverse reactions with each drug, please consult the manufacturer's product information.

Note: Bactrim single strength tablets were used in these clinical trials. However, studies have established the bioequivalency of one Bactrim DS tablet with two single strength Bactrim tablets.

actrim™
trimethoprim and 400 mg sulfamethoxazole)
lets

Bactrim DS™
(160 mg trimethoprim and 800 mg sulfamethoxazole)
Double Strength tablets

For chronic or frequently recurrent cystitis
pyelonephritis due to susceptible organisms.

For longer lasting results in chronic or frequently recurrent cystitis or pyelonephritis

Bactrim™

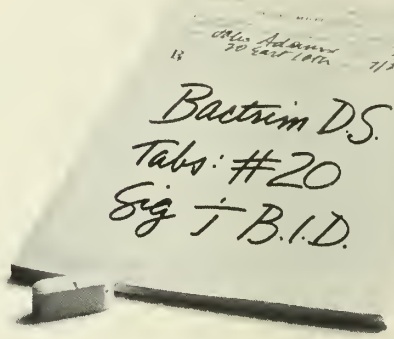
(80 mg trimethoprim and 400 mg sulfamethoxazole)

tablets

Bactrim™ DS

(160 mg trimethoprim and 800 mg sulfamethoxazole)

Double Strength tablets



Protocols

While results came from separate studies, protocols were identical with few exceptions:

Equivalencies: Patients selected were asymptomatic with chronic significant bacteriuria or had suffered a recurrence of previously treated symptomatic disease; significant bacteriuria was established as 100,000 or more of same organisms/ml urine in 2 consecutive cultures within 7 days; patient exclusions for reasons of safety or efficacy were identical; the same baseline laboratory studies were made at the same intervals; identical criteria were used to measure success or failure; clear culture was considered as 1000 or fewer organisms/ml urine.

Exceptions: Drug regimens differed (Study #1, two Bactrim tablets b.i.d. or one 500-mg ampicillin capsule q.i.d. for 10 days; Study #2, one 250-mg cephalexin pulvule q.i.d. for 28 days); pretreatment organisms had to be susceptible to ampicillin or cephalexin, but not necessarily to Bactrim.

For more detailed information on the two separate multicenter studies (see previous pages) in which Bactrim achieved better results than ampicillin or cephalexin in maintaining clear cultures, write to:

Professional Services Department
Roche Laboratories
Division of Hoffmann-La Roche Inc
Nutley, New Jersey 07110

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Chronic urinary tract infections evidenced by persistent bacteriuria (symptomatic or asymptomatic), frequently recurrent infections (relapse or reinfection), or infections associated with urinary tract complications, such as obstruction. Primarily for cystitis, pyelonephritis or pyelitis due to susceptible strains of *E. coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris* and *Proteus morganii.*

NOTE: The increasing frequency of resistant organisms limits the usefulness of antibacterials, especially in these urinary tract infections. The recommended quantitative disc susceptibility method (*Federal Register, 37*:20527-20529, 1972) may be used to estimate bacterial susceptibility to Bactrim. A laboratory report of "Susceptible to trimethoprim-sulfamethoxazole" indicates an infection likely to respond to Bactrim therapy. If infection is confined to the urine, "Intermediate susceptibility" also indicates a likely response. "Resistant" indicates that response is unlikely.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy; nursing mothers.

Warnings: Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted. **Data are insufficient to recommend use in infants and children under 12.**

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L. E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for children under 12. Usual adult dosage: 1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days.

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) every 24 hours
Below 15	Use not recommended

Supplied: Double Strength (DS) tablets, each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100; Tel-E-Dose packages of 100. Tablets, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole — bottles of 100 and 500; Tel-E-Dose packages of 100; Prescription Paks of 40, available singly and trays of 10.

Oral suspension, containing in each teaspoonful (5 ml) the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole; fruit licorice flavored — bottles of 16 oz (1 pint).

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Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

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e.g.: the pain of
surgical convalescence

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unlike acetaminophen/codeine combinations, it does not sacrifice anti-inflammatory action

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North Carolina 27709

IN GONORRHEA

INJECTION

Wycillin®

(STERILE PENICILLIN G PROCAINE SUSPENSION) WYETH

In **Gonorrhea,** the drug regimen of choice is aqueous penicillin G procaine. In uncomplicated cases, administration of 4.8 million units together with 1 gram oral probenecid, given just before injection, is recommended.

℞ **Indications:** In treatment of moderately severe infections due to penicillin G-sensitive microorganisms sensitive to the low and persistent serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: When high sustained serum levels are required use aqueous penicillin G, IM or IV.

The following infection will usually respond to adequate dosages of intramuscular penicillin G procaine—*N. gonorrhoeae:* acute and chronic (without bacteremia).

For deep intramuscular injection only.

Contraindication: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well-documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents, e.g., pressor amines, antihistamines, and corticosteroids.

Immediate toxic reactions to procaine may occur in some individuals, particularly when a large single dose is administered in the treatment of gonorrhea (4.8 million units). These reactions may be manifested by mental disturbances, including anxiety, confusion, agitation, depression, weakness, seizures, hallucinations, combativeness, and expressed "fear of impending death". The reactions noted in carefully controlled studies occurred in approximately one in 500 patients treated for gonorrhea. Reactions are transient, lasting from 15-30 minutes.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 ml. of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparations should not be used. Antihistaminics appear beneficial in treatment of procaine reactions.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy, discontinue penicillin and take appropriate measures.

If allergic reaction occurs, withdraw penicillin unless in the opinion of the physician, the condition being treated is life threatening and amenable only to penicillin therapy.

When treating gonococcal infections with suspected primary or secondary syphilis, perform proper diagnostic procedures, including darkfield examinations. In all cases in which concomitant syphilis is suspected, perform monthly serological tests for at least four months.

Adverse Reactions: (Penicillin has significant index of sensitization) skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; serum sickness-like reactions, including chills, fever, edema, arthralgia and prostration. Severe and often fatal anaphylaxis has been reported. (See "Warnings.")

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Procaine toxicity manifestations have been reported (see "Warnings"). Procaine hypersensitivity reactions have not been reported with this drug.

Dosage and Administration: Administer only by *deep intramuscular injection,* in upper outer quadrant of buttock. In infants and small children, midlateral aspect of thigh may be preferable. When doses are repeated, vary injection site. Before injection, aspirate to be sure needle bevel is not in blood vessel. If blood appears, remove needle and inject in another site.

Although some isolates of *Neisseria gonorrhoeae* have decreased susceptibility to penicillin, this resistance is relative, not absolute, and penicillin in large doses remains the drug of choice. Physicians are cautioned not to use less than recommended doses.

Gonorrheal infections (uncomplicated)—Men or Women: 4.8 million units intramuscularly divided into at least two doses and injected at different sites at one visit, together with 1 gram of oral probenecid, given just before injection.

NOTE: Treatment of severe complications of gonorrhea should be individualized using large amounts of short-acting penicillin. Gonorrheal endocarditis should be treated intensively with aqueous penicillin G. Prophylactic or epidemiologic treatment for gonorrhea (male and female) is accomplished with same treatment schedules as for uncomplicated gonorrhea.

Retreatment: The National Center for Disease Control, Venereal Disease Branch, U.S. Dept. H.E.W. recommends:

Test cure procedures at approximately 7-14 days after therapy. In the male, a gram-stained smear is adequate if positive; otherwise, a culture specimen should be obtained from the anterior urethra. In the female, culture specimens should be obtained from both the endocervical and anal canal sites.

Retreatment in males is indicated if urethral discharge persists 3 or more days following initial therapy and smear or culture remains positive. Follow-up treatment consists of 4.8 million units aqueous penicillin G procaine, I.M. divided in 2 injection sites at single visit.

In uncomplicated gonorrhea in the female, retreatment is indicated if follow-up cervical or rectal cultures remain positive for *N. gonorrhoeae.* Follow-up treatment consists of 4.8 million units aqueous penicillin G procaine daily on 2 successive days.

Syphilis: all gonorrhea patients should have a serologic test for syphilis at the time of diagnosis. Patients with gonorrhea who also have syphilis should be given additional treatment appropriate to the stage of syphilis.

Composition: Each disposable syringe 2,400,000 units (4-ml. size) contains penicillin G procaine in a stabilized aqueous suspension with sodium citrate buffer, and as w/v approximately 0.5% lecithin, 0.5% carboxymethylcellulose, 0.5% povidone, 0.1% methylparaben, and 0.01% propylparaben. The multiple-dose 10-ml. vial contains per ml. 300,000 units penicillin G procaine in a stabilized aqueous suspension with sodium citrate buffer and approximately 7 mg. lecithin, 2 mg. carboxymethylcellulose, 3 mg. povidone, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben, and 0.14 mg. propylparaben.

Five are graduating with honors. How many with VD?

On the average, you can figure the incidence of VD among teenagers at about 900 per 100,000 population.* And growing.

Among those in the 20-24 age-group, the incidence is even higher. And it, too, is growing.

In the long run, a populace educated to the risks and prevention of VD is probably the best answer to the problem. Meanwhile, though, adequate doses of the recommended types of penicillin remain a formidable weapon.

IN SYPHILIS
INJECTION
Bicillin® L-A
(STERILE PENICILLIN G BENZATHINE SUSPENSION) WYETH

Syphilis is preferably treated with penicillin G benzathine, which is also the drug of choice for prophylaxis after exposure. Administration of 2.4 million units (1.2 million in each buttock) usually cures most cases of primary, secondary and latent syphilis with negative spinal fluid.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular penicillin G benzathine.—Venereal infections: Syphilis, yaws, bejel and pinta.

For deep intramuscular injection only.

Contraindication: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens.

Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms including fungi. Take appropriate measures should superinfection occur.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness-like reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high doses of parenteral penicillin.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Dosage and Administration: Venereal infections—

Syphilis—Primary, secondary and latent—2.4 million units (1 dose).

Late (tertiary and neurosyphilis)—2.4 million units at 7 day intervals for three doses.

Congenital—under 2 years of age, 50,000 units/Kg. body weight; ages 2-12 years, adjust dosage based on adult dosage schedule.

(Shake multiple-dose vial vigorously before withdrawing the desired dose.) Administer by **deep intramuscular injection** in the upper outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site. Before injecting the dose, aspirate to be sure needle bevel is not in a blood vessel. If blood appears, remove the needle and inject in another site.

Composition: Units penicillin G benzathine (as active ingredient): 2,400,000 units in 4-ml. single dose disposable syringe. Each disposable syringe also contains in aqueous suspension with sodium citrate buffer, as w/v approximately 0.5% lecithin, 0.6% carboxymethylcellulose, 0.6% povidone, 0.1% methylparaben, and 0.01% propylparaben. 300,000 units per ml.—10-ml. multi-dose vial. Each ml. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. povidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben, and 0.14 mg. propylparaben.

Wyeth Laboratories
Philadelphia, Pa. 19101

U S Dept of Health, Education, and Welfare: VD Fact Sheet 1972. Publication No. (HSM) 73-8195.

(Continued from Page 8)

PHYSICIANS WANTED

TWENTY-SIX physician multispecialty clinic located in north suburban Milwaukee County seeking a second Board certified or eligible Orthopaedic Surgeon. Excellent facilities with 1.5 million dollar expansion program under way. Educational, cultural, recreational opportunities in the area to satisfy any desire. Guaranteed salary, bonus, malpractice insurance, profit sharing, fringe benefits, stockholder status after 2 years. Send Curriculum Vitae to J. R. Wrocklage, Director of Personnel, Milwaukee Medical Clinic, S.C., 3009 W. Good Hope Rd., Milwaukee, WI 53209.

MATURE CARDIOLOGIST needed to join busy solo consultant in Denver suburb. Full facilities (invasive and noninvasive) available. Write H. L. Kayser, MD, 8407 Bryant St., Westminster, Colorado 80030.

NEWBURY PARK (THOUSAND OAKS)-VENTURA COUNTY: Pediatrician, Internist, Family or General Practitioner needed in community of 20,000 population; 100,000 surrounding. Only medical bldg. and only doctors in area include OB-GYN group, dental group and optometrist. Beautiful area with numerous educational and recreational facilities. Fabulous opportunity. Contact: Dr. Berger or Dr. Resnik, 2904 Theresa Dr., Newbury Park, CA 91320. Phone: (805) 498-6631.

NEUROSURGEON WANTED—SOUTHEAST—Presently have part-time neurosurgeon in area and need another full-time one for our community. Population: City 45,000; county 80,000; drawing area 240,000. City located approx. 1½ hours from South's largest Metro area. Excellent school systems. Contact: Box No. 9463, Western Journal of Medicine, 731 Market St., San Francisco 94103.

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FULL-TIME ER PHYSICIAN—for modern, expanding, fully-accredited 467-bed regional medical center with low malpractice ins. rates, salary and fringes negotiable, progressive staff with specialty back up. Excellent schools, college facilities, cultural activities, recreational activities. Contact Dan S. Wilford, Adm., North Mississippi Medical Center, 830 South Gloster St., Tupelo, MS 38801; (601) 842-3632.

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M D

A physician seeking the challenge of improved patient care through the better use of health information systems, can look to this nonprofit, nongovernmental organization dedicated to the improvement of hospital and medical care. The position of **medical audit consultant**, free from the burdens of malpractice insurance and a high pressure environment, will involve some travel, public speaking, and interaction with many health care professionals.

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manager of employee relations
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SEEKING BOARD CERTIFIED OR QUALIFIED INTERNIST, preferably with subspecialty in allergy or gastroenterology, to associate with two established internists with subspecialties in cardiology and pulmonary diseases. New office building and facilities with unlimited land available for expansion across from a major hospital. Rapidly growing county seat-university-community college town on central coast of California; population 40,000 with 150,000 in area and several State institutions. Financial arrangements open and negotiable, eventual partnership desired. Completely equipped office includes lab, x-ray. Excellent fringe benefits and supporting staff. Beautiful multifaceted recreational and geographic area; good schools and churches. Send curiculum vitae to Box Number 9464, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

IMMEDIATE OPENING for full-time physician to join Medical Division of large international petrochemical company in Midwest. Board certified in internal medicine, or would consider board qualified. Salary negotiable, plus numerous company benefits. Anyone interested should respond to Phillips Petroleum Company, Medical Director, B 57 Adams Building, Bartlesville, OK 74004.

PHYSICIAN—Full and part-time opening in decentralized health clinics. Innovative total community health program. Unique opportunity to become involved in clinical, public, mental and rural health activities. Spanish fluency valuable. California license necessary. Contract range $37,000-$40,950. Contact Trevor D. Glenn, MD, Director of Health, 515 South Cedar Ave., Fresno, CA 93702 or call (209) 488-3743.

ARE YOU TIRED OF PAYING HIGH MEDICAL MALPRACTICE LIABILITY PREMIUMS? Wanted —Board certified or Board eligible physician with interest in chronic disease and rheumatology for 100-bed rehabilitation hospital and 250-residential rehabilitation center in attractive country area; housing and recreational facilities provided; liberal fringe benefits. Contact Chief of Staff, Georgia Warm Springs Hospital, Warm Springs, Georgia 31830. Telephone (404) 655-3321.

MONTANA—WOLF POINT—URGENTLY NEEDS PHYSICIANS—Present physicians two (2)—Each seeking associates—Or community will cooperate on your needs to establish a private practice —Financial assistance available—Trade area of 15,000 — Sportsman's paradise — Wide open spaces—Good place to raise a family—Excellent schools—50-bed hospital—Contact the Wolf Point Chamber of Commerce and Agriculture. Phone (406) 653-2012.

MEDICAL DIRECTOR—MD to fill executive medical director position in a large and aggressive H.M.O. Must have strong leadership capability, clinical exp. Exp. in peer-review and quality control. Salary and benefits open. Call Dr. Reiner (714) 264-3153. Please write résumé to 6601 Imperial Ave., San Diego, CA 92114.

GENERAL PRACTITIONERS READY TO RELOCATE? Atwood, Kansas in sunny northwest Kansas is an ideal location. Modern hospital with complete Lab, X-ray and other ancillary services. A community of 1,800 and service area of 5,000 friendly people. Recreational opportunities, fine schools, and low medical malpractice rates. Contact Jeff Reinert, P.O. Box 47, Atwood, Kansas 67730.

(Continued on Page 19)

ASSOCIATE MEDICAL DIRECTOR

Major Life Insurance Company with headquarters in a highly desirable Southern California area seeks an Assistant or an Associate Medical Director. Ideally, the successful candidate would have some life insurance industry experience. It would also be desirable that the candidate would have had some private practice background in the general or internal medicine field. However, experience in occupational medicine or public health would also be acceptable. Compensation open and commensurate with experience. Please contact in complete confidence our Professional Executive Recruiting Consultants:

HERGENRATHER & COMPANY
3435 Wilshire Boulevard, Suite 2128
Los Angeles, CA 90010
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	1971	1972	1973	1974	1975
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Escherichia coli	99%	99%	99%	99%	99%
Proteus species, indole-negative	98%	99%	99%	99%	99%
Proteus species, indole-positive	97%	96%	94%	94%	92%
Pseudomonas aeruginosa	96%	96%	95%	94%	95%
Klebsiella-Enterobacter-Serratia	99%	98%	99%	99%	98%
Staphylococcal Susceptibility No. of Patient Isolates	97% 6,995	98% 11,109	98% 12,225	99% 18,352	99% 28,130
Staphylococcus aureus	97%	98%	98%	99%	99%
Staphylococcus epidermidis	97%	97%	98%	98%	98%

Source: PMR Bacteriologic Reports—1971-1975.
These *in vitro* data are based on results obtained from a nationwide panel of 180 acute-care hospitals of 100 beds or more. All hospitals in the audit used the Kirby-Bauer method of disc sensitivity. Data are presented in unweighted form.

***In vitro* susceptibility data are not necessarily indicative of clinical effectiveness.**

See Clinical Considerations section which follows...

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WARNING

Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

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GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.

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In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY Safety for use in pregnancy has not been established.

INDICATIONS GARAMYCIN Injectable is indicated, with due regard for relative toxicity of antibiotics, in the treatment of serious infections caused by susceptible strains of the following microorganisms:

Pseudomonas aeruginosa, Proteus species (indole-positive and indole-negative), *Escherichia coli* and *Klebsiella-Enterobacter-Serratia* species.

Clinical studies have shown GARAMYCIN Injectable to be effective in septicemia and serious infections of the central nervous system (meningitis), urinary tract, respiratory tract, gastrointestinal tract, skin and soft tissue (including burns).

Bacteriologic tests to determine the causative organisms and their susceptibility to gentamicin should be performed.

Bacterial resistance to gentamicin develops slowly in stepwise fashion; there have been no one-step mutations to high resistance.

In suspected or documented gram-negative sepsis, GARAMYCIN may be considered as initial therapy. The decision to continue therapy with this drug should be based on the results of susceptibility tests, the severity of the infection, and the important additional concepts contained in the Warning Box.

For suspected sepsis when the infecting organism is unknown, gentamicin may be administered in conjunction with a penicillin-type drug. Following identification of the organism and its susceptibility, appropriate antibiotic therapy should then be continued. In the neonate with suspected sepsis or staphylococcal pneumonia, a penicillin-type drug is also usually indicated as concomitant therapy with gentamicin.

GARAMYCIN Injectable has been shown to be effective in serious staphylococcal infections. It may be considered in those infections when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility testing and clinical judgment indicate its use.

CONTRAINDICATIONS A history of hypersensitivity to gentamicin is a contraindication to its use.

WARNINGS See Warning Box.

PRECAUTIONS Neuromuscular blockade and respiratory paralysis have been reported in the cat receiving high doses (40 mg./kg.) of gentamicin. The possibility of these phenomena occurring in man should be considered if gentamicin is administered to patients receiving neuromuscular blocking agents, such as succinylcholine and tubocurarine.

Treatment with gentamicin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy is indicated.

ADVERSE REACTIONS:

Nephrotoxicity: Adverse renal effects, as demonstrated by rising BUN, NPN, serum creatinine and oliguria, have been reported. They occur more frequently in patients with a history of renal impairment treated with larger than recommended dosage.

Neurotoxicity: Adverse effects on both vestibular and auditory branches of the eighth nerve have been reported in patients on high dosage and/or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss.

Numbness, skin tingling, muscle twitching, and convulsions have also been reported.

Note: The risk of toxic reactions is low in patients with normal renal function who do not receive GARAMYCIN Injectable at higher doses or for longer periods of time than recommended.

Other reported adverse reactions, possibly related to gentamicin, include increased serum transaminase (SGOT, SGPT), increased serum bilirubin, transient hepatomegaly, decreased serum calcium; splenomegaly, anemia, increased and decreased reticulocyte counts, granulocytopenia, agranulocytosis, thrombocytopenia, purpura; fever, rash, itching, urticaria, generalized burning, joint pain, laryngeal edema; nausea, vomiting, headache, increased salivation, lethargy and decreased appetite, weight loss, pulmonary fibrosis, hypotension and hypertension.

DOSAGE AND ADMINISTRATION

GARAMYCIN Injectable may be given intramuscularly or intravenously.

For Intramuscular Administration:

*Patients with normal renal function**

Adults: The recommended dosage for GARAMYCIN Injectable for patients with serious infections and normal renal function is 3 mg./kg./day, administered in three equal doses every 8 hours.

For patients weighing over 60 kg. (132 lb.), the usual dosage is 80 mg. (2 ml.) three times daily. For patients weighing 60 kg. (132 lb.) or less, the usual dosage is 60 mg. (1.5 ml.) three times daily.

In patients with life-threatening infections, dosages up to 5 mg./kg./day may be administered in three or four equal doses. This dosage should be reduced to 3 mg./kg./day as soon as clinically indicated.

**In children and infants, the newborn, and patients with impaired renal function, dosage must be adjusted in accordance with instructions set forth in the Package Insert.*

For Intravenous Administration:

The intravenous administration of GARAMYCIN Injectable is recommended in those circumstances when the intramuscular route is not feasible (e.g., patients in shock, with hematologic disorders, with severe burns, or with reduced muscle mass).

For intravenous administration in adults, a single dose of GARAMYCIN Injectable may be diluted in 100 or 200 ml. of sterile normal saline or in a sterile solution of dextrose 5% in water; in infants and children, the volume of diluent should be less. The concentration of gentamicin in solution in both instances should normally not exceed 1 mg./ml. (0.1%). The solution is infused over a period of one to two hours.

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GARAMYCIN Injectable should not be physically premixed with other drugs, but should be administered separately in accordance with the recommended route of administration and dosage schedule.

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SLS-583

(Continued from Page 16)

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(Continued on Page 22)

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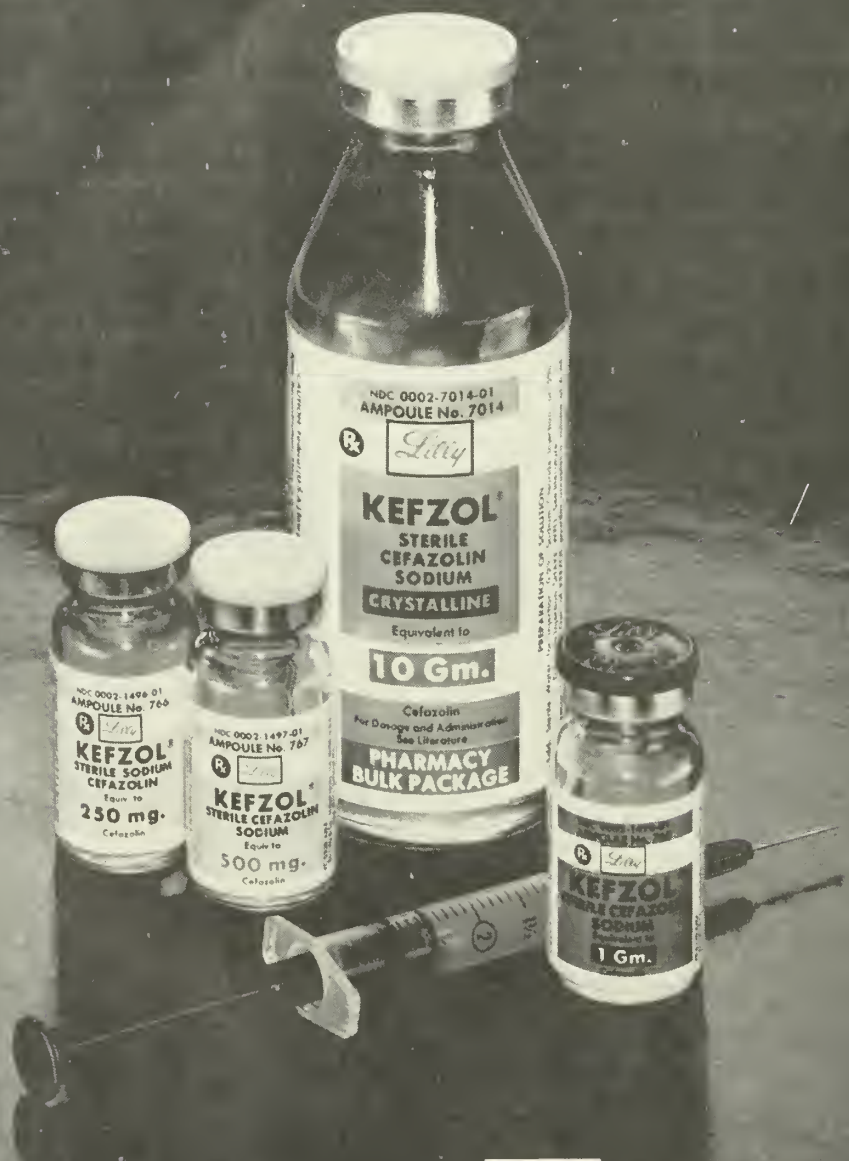

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Refer to: Goodman JM, Bischel MD, Wagers PW, et al: Barbiturate intoxication—Morbidity and mortality. West J Med 124:179-186, Mar 1976

THE WESTERN
Journal of Medicine

Barbiturate Intoxication

Morbidity and Mortality

JAY M. GOODMAN, MD, *Los Angeles;* MARGARET D. BISCHEL, MD, *Park Ridge, Illinois;* PARK W. WAGERS, MD, *and* BENJAMIN H. BARBOUR, MD, *Los Angeles*

The complications encountered in caring for 185 patients intoxicated with barbiturates were reviewed. The population consisted of 142 patients with long-acting barbiturate concentrations of 8 mg per 100 ml or greater, 20 patients with short-acting barbiturate concentrations of 3 mg per 100 ml or greater and 23 consecutive patients with short-acting barbiturate intoxication referred for monitoring. Pneumonia was the major cause of morbidity and mortality and correlated best with the initial depth of coma and the use of an endotracheal tube in treatment. Cardiovascular instability manifested by pulmonary edema was the next leading cause of morbidity and mortality and correlated best with the initial depth of coma and the quantity of intravenous fluid administered. In retrospect, use of eliminative measures such as dialysis would probably not have altered the outcome in most of the patients who died and attempts at forced diuresis may have contributed to several deaths. Particular emphasis should be placed on the problems of sepsis and fluid therapy in the management of these patients.

CURRENT RECOMMENDED therapy for the treatment of barbiturate intoxication consists of meticulous supportive care[1-5] with or without aggressive measures to remove barbiturate from the body[6-13] (gastric lavage, forced diuresis, peritoneal dialysis and hemodialysis). An unexpectedly frequent occurrence of pneumonia and fluid overload in those patients who were severely intoxicated prompted a critical review of the current therapy for barbiturate intoxication at the Los Angeles County-University of Southern California (LAC-USC) Medical Center. In an attempt to evaluate the cases of the most severely intoxicated patients, one group with long-acting and one with short-acting barbiturate intoxications were retrospectively selected on the basis of potentially lethal serum barbiturate concentrations.[14-15] To better document fluid overload, a limited prospective study was undertaken involving more careful monitoring of cardiovascular function.

From the Department of Medicine, Los Angeles County/University of Southern California Medical Center, Los Angeles.

Submitted June 13, 1975.

Reprint requests to: Margaret Bischel, MD, Director, Medical Education, Lutheran General Hospital, 1775 Dempster St., Park Ridge, IL 60068.

Methods

The clinical course and laboratory data of the following patients admitted to hospital for barbiturate intoxication at LAC-USC Medical Center were grouped and analyzed as follows: *Group I*

ABBREVIATIONS USED IN TEXT

CPK = creatine phosphokinase
LAC-USC = Los Angeles County-University of Southern California (medical center)
LDH = lactic dehydrogenase
LDH_1, LDH_2, LDH_5 = serum cardiac LDH isoenzymes
SGOT = serum glutamic oxaloacetic transaminase

—142 patients with serum long-acting barbiturate concentrations of 8 mg per 100 ml or greater on admission, *Group II*—20 patients with serum short-acting barbiturate concentration of 3 mg per 100 ml or greater on admission and *Group III*—23 consecutive patients referred for short-acting barbiturate intoxication (0.2 to 4.3 mg per 100 ml) who were prospectively studied. Cases were located by reviewing the LAC-USC Medical Center toxicology records in Groups I and II, or by referral for Group III. In all patients admitted with a suspected drug overdosage, a hypnotic screen and determination of blood barbiturate levels are routinely done.

All cases were grouped into the admitting stage of coma after an adequate airway was established.[16] The coma stages were:

- *Stage 0*—Not in coma.
- *Stage 1*—Response to painful stimuli. Deep tendon reflexes present. Gag reflex. Blood pressure normal and stable. Respiration adequate.
- *Stage 2*—No response to painful stimuli. Deep tendon reflexes present. Blood pressure normal and stable. Respiration adequate but slow rate.
- *Stage 3*—No response to painful stimuli. Deep tendon reflexes absent. Gag reflex present or absent. Respiration adequate but slow rate.
- *Stage 4*—No response to painful stimuli. Deep tendon reflexes absent. Blood pressure unstable and needs support or respiration inadequate and needs support or both.

Pneumonia was diagnosed by the criteria of fever, leukocytosis, purulent sputum and an infiltrate on x-ray film of the chest; specific bacteriologic diagnosis was not required. Antibiotics were administered only after pneumonia or other bacterial infection was evident. Endotracheal intubation was routine during gastric lavage to protect the airway. Intubation was also carried out when necessary to improve bronchopulmonary toilet and provide respiratory support. Hospital policy recommended gastric lavage and lavage was carried out in most patients in Stage 1 through 4 coma.

Cardiovascular instability was diagnosed by any of the following criteria: protodiastolic ventricular gallop (S_3), central venous pressure over 10 cm of water measured with the respirator disconnected or findings on an x-ray film of the chest showing either redistribution of pulmonary arterial flow to the upper lobes or gross pulmonary edema.

Serum barbiturate concentrations were determined at the LAC-USC Medical Center spectrophotometrically by a modification of the method of Goldbaum.[17] Whole blood counts were determined by Coulter counter. Serum glutamic oxaloacetic transaminase (SGOT) was determined by the method of Karman, Wroblewski and LaDue[18] with results expressed in Wroblewski-LaDue units. Alkaline phosphatase was determined by the method of Bessey, Lowry and Brock[19] and expressed in Bessey-Lowry units. Aldolase was measured enzymatically by BioScience Laboratories.[20] Lactic dehydrogenase (LDH) was measured by the Trayser-Seligson modification of the Wroblewski-LaDue method[21] and expressed in Henry units. LDH isoenzymes were determined by the method of DiGiorgio.[22] The percentages were normalized by multiplying each fraction by the total LDH. Creatine phosphokinase (CPK) was assayed by the Rosalki method[23] and expressed in Henry units. Statistical analysis was done by the method of analysis of variance and trend analysis for populations of three or more groups.

TABLE 1.—*Long-Acting Barbiturate Concentrations of 8 mg per 100 ml or Greater*

Stage	Number of Patients	Age	Barbiturate Range	Barbiturate Average±S.D.
0	70	1-69	8-20	10.53±2.50
1	34	5-53	8.1-16	10.22±2.17
2	13	26-51	8.2-31.1	13.59±6.40
3	16	14-83	8.2-22.7	13.64±4.76
4	9	18-50	12-31.7	22.16±6.13

TABLE 2.—*Incidence of Temperature >100°F, Pneumonia and Death in Patients with Long-Acting Barbiturate Concentrations of 8 mg per 100 ml or Greater*

Stage	Number of Patients	Temp >100°F	Pneumonia	Deaths
0	70	6 (9%)	3 (4%)	0
1	34	11 (32%)	3 (9%)	0
2	13	11 (85%)	10 (77%)	1 (8%)
3	16	15 (94%)	12 (75%)	2 (12%)
4	9	9 (100%)	9 (100%)	1 (11%)
	142	52 (37%)	37 (26%)	4 (3%)

TABLE 3.—*Cardiovascular Instability Correlated with Intravenous Fluids Exceeding 240 ml per Hour for Patients with Long-Acting Barbiturate Concentrations of 8 mg per 100 ml or Greater*

Stage	Number of Patients	Instability	Instability >240 ml/hr	Instability <240 ml/hr
0	70	1 (1%)	0/1	1/69 (1%)
1	34	1 (3%)	1/3 (33%)	0/31
2	13	1 (8%)	1/5 (20%)	0/8
3	16	3 (17%)	3/9 (33%)	0/7
4	9	6 (67%)	6/7 (86%)	0/2
	142	12 (9%)	11/25 (44%)	1/117 (1%)

TABLE 4.—*Short-Acting Barbiturate Concentrations of 3 mg per 100 ml or Greater*

Stage	Number of Patients	Age	Barbiturate Range	Barbiturate Average±S.D.
0	1	22	4.5	4.50
1	1	29	4.1	4.10
2	5	13-40	3.0-3.8	3.36± .34
3	5	20-55	3.1-5.2	3.82± .74
4	8	1-41	3.3-7.5	4.66±1.28

The cases in Group III were studied in greater detail to evaluate cardiovascular and metabolic function. In addition to the data collected for the other groups, each subject had the following data monitored and analyzed: highest body temperature, admission and peak serum CPK, LDH and LDH isoenzymes, aldolase, barbiturates, arterial oxygen pressure (Po_2) on admission, venous lactate, hemoglobin, and daily electrocardiograms (EKG's). The EKG's were read by one of the authors (B.H.B.) without knowledge of the clinical course and scored as normal or abnormal on the basis of QRS-T morphology. The patients in Stage 2 and Stage 3 coma were deleted from statistical analysis because of their small number.

Results

Group I—Long-acting barbiturate, 8 mg per 100 ml or greater

The patients' ages ranged from 1 to 83 years and were equally distributed among the stages of coma. There was a large overlap between the serum barbiturate concentrations in each stage of coma (Table 1).

During time in hospital, pneumonia and a temperature above 100°F (37.8°C) were more common as the stage of coma increased ($p<.01$) (Table 2). One patient in Stage 1 coma, six of 13 in Stage 2, nine of 16 in Stage 3, and all nine patients in Stage 4 were endotracheally intubated. In 24 of these 25 patients, pneumonia developed. In 13 of the 117 patients not intubated pneumonia developed—3 not in coma, 2 in Stage 1, 3 in Stage 2 and 5 in Stage 3 ($p<.001$) (Figure 1). The number of days the patients remained intubated did not correlate with drug concentration ($r=.3$, $p=$n.s. [r is the correlation coefficient; p is the probability; n.s. means not significant]).

TABLE 5.—*Incidence of Temperature of 100°F, Pneumonia and Death in Patients with Short-Acting Barbiturate Concentrations of 3 mg per 100 ml or Greater*

Stage	Number of Patients	Temperature 100°F	Pneumonia	Death
0	1	0	0	0
1	1	0	0	0
2	5	4 (80%)	2 (40%)	0
3	5	4 (80%)	2 (40%)	0
4	8	8 (100%)	8 (100%)	1 (13%)
	20	16 (80%)	12 (60%)	1 (5%)

In 11 of 25 patients who received more than 240 ml per hour of intravenous fluid for at least eight hours, signs of cardiovascular instability (as previously defined) were recorded. In only one of 117 patients who received less than 240 ml per hour were such signs recorded ($p<.05$) (Table 3).

One patient in Stage 2, two in Stage 3 and one in Stage 4 died. Three deaths were due to pneumonia and one was due to pulmonary edema. The death due to pulmonary edema occurred in a 45-year-old man in Stage 2 coma (8.2 mg per 100 ml serum concentration) who received 250 ml per hour of alkalinized intravenous fluid for 24 hours. Autopsy confirmed pulmonary edema as the only significant pathological feature.

Group II—Short-acting barbiturate, 3 mg per 100 ml or greater

Neither the patients' ages (range 1 to 55 years) nor the serum barbiturate concentration (range 3.0 to 7.5 mg per 100 ml) was significantly different among the coma stages (Table 4). The incidence of pneumonia and temperature above 100°F increased as the stage of coma deepened ($p<.05$) (Table 5). The number of days the patients remained intubated did not correlate with the serum barbiturate concentration ($r=.47$, $p=$n.s.). In 12 of 16 intubated patients, pneumonia developed while it developed in none of the four nonintubated patients ($p<.05$) (Figure 2). Cardiovascular instability was recorded in four patients, all in Stage 4 coma, aged 17, 30, 31 and 33 years. One patient in this group died because of pneumonia.

Group III—Short-acting barbiturates

The patients' ages ranged from 17 to 67 years and did not differ among the stages. Of the 23 cases of short-acting barbiturate intoxication, six were in Stage 1 coma, two in Stage 2, two in Stage 3 and 13 in Stage 4. The Stage 4 patients were classed in subgroups by absence (4A) or presence (4B) of cardiovascular instability using the previously mentioned criteria.

Mean serum barbiturate concentration was different for these stages when analyzed by variance and trend analysis in the ascending order of 1, 4A and 4B ($p<.05$) (Table 6). The serum cardiac isoenzyme concentrations (LDH 1 and LDH 2) were likewise statistically weighted to group 4B ($p<.05$) (Table 7). Moreover, in all eight of the patients in 4B, there were abnormal findings on electrocardiograms characterized by S-T segment changes; but in only one of six patients in Stage 1 were there abnormal findings on electrocardiograms. Similarly, the incidence of pneumonia and temperatures above 100°F increased with higher levels of coma ($p<.05$) (Table 6). The mean LDH, CPK, SGOT, LDH_5 and aldolase values were higher in the 4B patients, but failed to reach statistical significance ($.1>p>.05$) (Table 7).

The patients' admission arterial Po_2 measured while breathing room air ranged from 72 to 37 mm of mercury and did not correlate with stage of coma. None of these patients died.

In all but one of these patients there was a fall in hemoglobin concentration during one to five days in hospital. The mean initial hemoglobin concentration was 14.39 grams per 100 ml±.46 (S.E.M.) and the lowest mean concentration was 12.16 grams per 100 ml ($p<.01$). In none of these patients was there gastrointestinal blood loss or evidence of hemolysis. Phlebotomy never exceeded 80 ml on admission or 40 ml on each subsequent day. The total fall in hemoglobin correlated with the number of days until the nadir of the hemoglobin concentration occurred (Figure 3) ($r=.71$, $p<.05$). The largest falls occurred in the 48 patients.

Pooled data from Groups I through III

In both short- and long-acting barbiturate intoxication, the incidence of pneumonia increased with the initial depth of coma. For both intoxications the use of an endotracheal tube correlated with a greater incidence of pneumonia. Despite the generally shorter duration of coma for short-acting barbiturate intoxication, the incidence of pneumonia is comparable regardless of the drug or duration of coma when one simply considers the initial stage of coma (Figures 1, 2). Of the 63 cases of pneumonia in the entire series, the following aerobic bacterial sputum isolates were noted in 19: Staphylococcus aureus, 7; Escherichia coli, 3; Klebsiella, 3; Serratia, 1; Pseudomonas aerogenes, 2; Streptococcus faecalis, 1, and Enterobacteriaceae, 3.

Discussion

Pneumonia, cardiovascular instability and high serum barbiturate concentrations are uniform problems regardless of the type of barbiturate ingested. For this reason, the data are discussed in terms of major problems rather than separating the short- from the long-acting barbiturate intoxications. Parallel incidences of each problem in each group occurred in this series.

- *Pulmonary infection* is the major cause of morbidity and mortality in all groups. The aerobic bacterial organisms cultured are typically virulent and mixed. At the time of study, effective means of anaerobic culturing were not available; such data may be quite relevant.[24] Potential factors contributing to pneumonia include prior aspiration,[25] inadequate tracheal toilet, prolonged respi-

TABLE 6.—*Coma Stage Compared with Serum Short-Acting Barbiturate Concentration and Other Clinical Variables*

	Stage 1	*Stages 2-3*	*Stage 4A*	*Stage 4B*
Number of patients	6	2 stage 2 2 stage 3	5	8
Age±S.E.M.	36±6	22±3	29±5	34±6
Sex	4M—2F	1M—3F	2M—3F	4M—4F
Barbiturate concentration (per 100 ml)*	1.1±.2	2.5±.4	1.8±.2	2.7±.4
Pneumonia	1	2	1	3
Temperature 100°F	1	2	1	3
Patients intubated	1	3	5	8
Cardiovascular instability	0	0	0	8

*Probability .05.

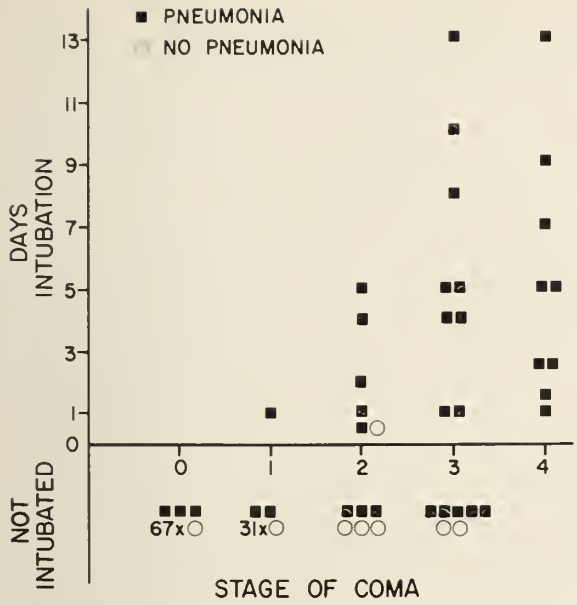

Figure 1.—Presence of pneumonia correlated with stage of coma and days of intubation for long-acting barbiturate concentrations of 8 mg per 100 ml or greater (probability <.001).

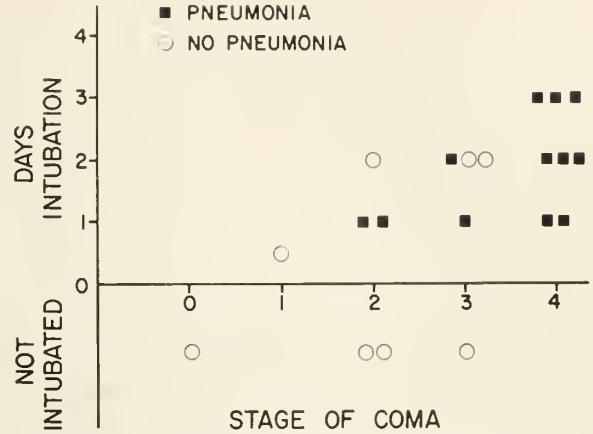

Figure 2.—Presence of pneumonia correlated with stage of coma and days of intubation for short-acting barbiturate concentrations of 3 mg per 100 ml or greater.

rator dependence, nosocomial contamination,[26] and perhaps unknown defects in host defense mechanisms secondary to the insult of intoxication, hypoxia and hypotension. Some of these patients may have also ingested alcohol, which has been shown to inhibit phagocytic activity.[27-29] It is unknown whether barbituric acid alone can alter phagocytic function.

The striking incidence of pneumonia seen in the endotracheally intubated patients (96 percent in Group I, 75 percent in Group II and 35 percent in Group III) compared to the nonintubated patients (11 percent in Group I, 0 percent in Group II and 17 percent in Group III) can be interpreted two ways. First, it is possible that the care of these patients was inadequate to prevent pneumonia. The data of Haberman and coworkers[30] documenting the difficulty of performing adequate tracheal suctioning through an endotracheal tube is pertinent to this issue. Second, the severity of the illness necessitating the intubation indicates that these patients were prime candidates for a prior aspiration[31] or subsequent pneumonia. These two possibilities cannot be differentiated from the data.

Although in the patients with short-acting barbiturate intoxication there was a shorter duration of coma than in those with long-acting intoxication, the incidence of pneumonia was comparable for each stage of coma. The only factors that correlated with pneumonia were the initial stage of coma and the use of an endotracheal tube in management. However, use of an endotracheal tube is usually necessary in Stage 4 coma and

TABLE 7.—*Coma Stage Compared with Laboratory and Electrocardiographic Changes*

	Stage 1	*Stages 2-3*	*Stage 4A*	*Stage 4B*
Number of patients	6	4	5	8
Po_2 (mm Hg) ±S.E.M.	59±7	54±8	56±4	54±2
Lactate (mg per 100 ml)	35±22	16±5	10±4	28±19
CPK(initial) (Henry units)	12±7	2.6±1.0	1.8±.6	231±180
CPK(maximum)	14±10	15±7	2.4±.7	346±183
LDH(maximum) (Henry units)	451±62	500±78	408±32	1,746±427
LDH_1 (Henry units)*	101±11	96±8	80±16	154±19
LDH_2*	115±16	151±26	117±10	220±37
LDH_5†	77±19	96±18	53±11	371±139
SGOT (Wroblewski-La Due units)†	36±11	38±11	38±12	493±254
Alkaline phosphatase (Bessey-Lowry units)	2.3±.4	2.9±.4	2.7±.1	3.9±.7
Aldolase†	47±8	38±7	35±6	266±101
Patients with abnormal findings on EKG's*	1	0	2	8

*Probability <.05.
†Probability <.1.
Po_2 = arterial oxygen pressure
CPK = creatine phosphokinase
LDH = lactic dehydrogenase
LDH_1, LDH_2 LDH_5 = serum LDH isoenzymes
SGOT = serum glutamic oxaloacetic transaminase
EKG = electrocardiogram

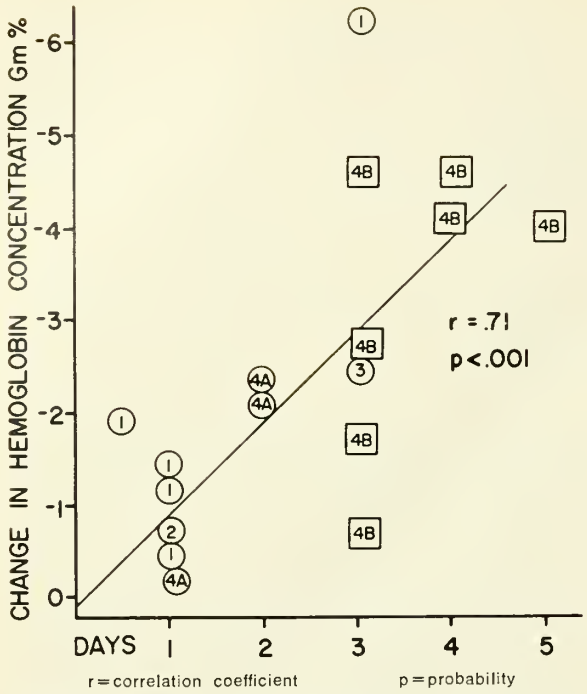

Figure 3.—Decrease from admission hemoglobin concentration correlated with the number of days until this lowest value occurred. Each patient is represented by his admission level of coma. Patients in Stage 4B showed signs of cardiovascular instability.

may be indicated in less severely intoxicated patients.

Prior aspiration or the total host insult seems to make pneumonia almost a certainty for the severely intoxicated intubated patient even if he remains in coma only 24 hours, as was the case in several Stage 4 short-acting barbiturate intoxications. Early in the hospital course, a patient's temperature exceeding 100°F should alert the physician to the likelihood of a developing pneumonia. Whether this is initially a chemical pneumonia or an actual bacterial pneumonia is unknown, but in most of the patients true bacterial pneumonia was eventually seen.

• We have observed a group of patients who have clinical manifestations of *fluid volume overload* and diffuse interstitial fluid accumulation including lung, abdominal viscera and skin. Depth of coma and the quantity of administered intravenous fluid are the major predisposing factors. Frequent weight determinations as well as careful attention to records of intake and output should improve clinical management.

The data suggest three potential cardiovascular defects which might explain why in these patients interstitial edema accumulates. First, there may be myocardial function impairment[32] in severely intoxicated patients stemming from the total overdose insult, or rarely, underlying organic heart disease. The significant leak of cardiac LDH isoenzymes and the frequency of abnormal findings on electrocardiograms in patients in whom there is inability to handle a fluid load (240 ml per hour) infers acute cardiac impairment. Despite the liberal criteria we have employed for cardiovascular instability, the circumstantial evidence is highly suggestive of inadequate myocardial function. Shubin and Weil[33] have previously rebutted the supposition that the initial hypotension seen in most of these patients reflects pump failure by showing that their cardiac index rises to "normal" with volume replacement. It is noteworthy that after volume replacement their fatalities had a significantly lower cardiac index, mean arterial pressure and urinary output than those who survived.[34] We can only reconcile our two conclusions by suggesting that a "normal" cardiac index is probably inadequate for these patients who are frequently septic, febrile, hypotensive and undergoing a fluid challenge.

Second, Shubin and co-workers[33] have suggested that the venous capacitance bed is expanded in these patients and attribute the initial hypotension to this defect. They suggest that copious intravenous fluids can overcome this initial problem. Their data support the hypothesis of an expanded capacitance bed by showing a fall in mean hemoglobin concentration, an increase in plasma volume index but no change in the red cell index with intravenous fluid therapy.[34] If this were the only mechanism in operation, one would expect to see an initial fall in hemoglobin concentration that would remain stable after the vascular space was re-expanded. The continued fall of hemoglobin over one to five days in the absence of blood loss or hemolysis is consistent with further dilutional changes stemming from a progressively expanding vascular bed. This could be a result of over-vigorous intravenous therapy or relate to other continuing neurohumeral mechanisms which cause this vascular bed to continue to expand even as the drug concentration is diminishing. No data exist concerning the renal or endocrine system responses to this clinical situation.

Third, interstitial edema may arise from an increased permeability of the vascular bed induced by a combination of the drug, hypotension, hypothermia, hypoxia and subsequent mechanical

ventilation. If such a defect exists, it would seem likely that copious fluid administration advocated for treatment of hypotension would increase the intravascular hydrostatic pressure and cause an increased leak of fluid.

Without invoking one or more of these hypotheses, it is difficult to understand why in so many presumably healthy young people pulmonary edema develops while fluid loads are being received which would easily be excreted under normal circumstances. This complication of therapy must be seriously considered in the management of these patients until further studies resolve the issue.

• Vigorous attempts have been made to hasten *barbiturate elimination* because it is assumed that the drug is the primary agent which causes the complications we have enumerated. Indications for such measures vary from the total ingested dose to the ingestion of multiple drugs including alcohol (information rarely available to the primary physician) to the serum barbiturate concentration, to the severity of the coma.[15] These data confirm what some authors[2] have previously noted—serum barbiturate concentration is a poor prognostic indicator in these patients. Alcohol and the sedative hypnotic drug should be surveyed in each case. In this series, neither the morbidity nor mortality of any group correlated with drug concentration. Drug withdrawal was not a clinical problem even in those who gave a history of chronic barbiturate abuse. Conversely, half of the patients in Group I were arousable with potentially "lethal concentrations."[14,15] For these reasons we do not feel either the amount of drug ingested or serum drug concentration alone constitutes grounds for aggressive eliminative therapy.

Advocates of vigorous eliminative therapy for severely obtunded patients have yet to present adequately controlled series to show that this technique actually lessens morbidity and mortality.[1] It is doubtful even in those cases where rapid drug removal is possible, that it would have improved the outcome of our deaths due to pneumonia in Group I or II.

Of the effective methods of drug elimination available, dialysis and alkaline diuresis are the most frequently used. Attempting hemodialysis in a hypotensive patient is technically difficult and potentially harmful if blood is shunted from other vital organs. Alkaline forced diuresis over 240 ml per hour invites fluid intolerance as a frequent and potentially lethal complication. Frequent reliable bed scale weights are difficult to obtain in most large clinical facilities, and even 240 ml per hour may prove excessive in some patients. In view of the conflicting data, we have yet to conclude that eliminative measures have a major role in the treatment of these patients.

The basic question which has been neglected in the past is "Why do these patients die?" Our data suggest three major problems in their management: first, pneumonia is the leading cause of morbidity and mortality regardless of the duration or cause of coma; second, over-vigorous hydration in severely obtunded patients is poorly tolerated and may lead to pulmonary edema and death, and, third, additional complications of therapy (pneumothorax, flail chest and so forth) compound an already difficult situation.

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Dealing with Nonspecific Diarrhea

In treating patients with nonbacterial diarrhea, there is no evidence whatsoever that nonabsorbable or absorbable antimicrobial agents produce any sort of beneficial effect. In fact, the reverse is true. Our studies in Central America have again shown that an average patient experiences a prolongation of diarrhea with any type of antimicrobial therapy. And thus, the blind use of diarrhea nostrums containing one or several nonabsorbable antibiotics (which is still widely practiced around the world) is to be condemned. Equally poor practice is the administration of systemic antimicrobial therapy. The situation can really be handled much more effectively by symptomatic treatment.

Most patients with mild to moderate diarrhea probably respond as quickly to rest and to the administration of a bland, clear liquid diet as they do to any type of pharmacologic therapy. Abdominal cramps will often be diminished in frequency or intensity by the local administration of heat—the old hot water bottle is still very useful. Occasionally, anticholinergic agents are beneficial for these complaints. In children, diphenhydramine (Benadryl®)—which combines an antihistaminic action with strong sedative action and an atropine-like effect—is used with reported success by many practitioners in our area for the relief of cramps. It sedates the child, it seems to be quite nontoxic and it has, apparently because of its atropine-like action, an anticramp effect. It, of course, does not affect the diarrhea per se.

I should particularly mention that diphenoxylate, or Lomotil®, should never be employed in small children. I know it is used for this purpose rather widely, but one has to recognize that the range between effective and toxic dosage is too small in young children.

—HEINZ F. EICHENWALD, MD, *Dallas*

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An Evaluation of Bilateral Breast Carcinoma

Simultaneous and Sequential Lesions

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The detection of bilateral breast carcinoma, simultaneous or nonsimultaneous, appears to be increasing. Undoubtedly a major factor in this is the increased use of mammography and xeromammography. In a 21-year period at Saint John's Hospital and Health Center, 1,189 cases of primary breast carcinoma were treated, of which 34 (2.9 percent) were bilateral. However, from 1972 to 1974 the incidence has risen from 1.9 to 10.8 percent, with a simultaneous rise in numbers of xeromammograms made. Xeromammography should be done routinely in patients in whom carcinoma of the breast is suspected. Its use should also be an integral part of the follow-up in patients in whom mastectomy has been carried out previously.

WHETHER THE INCREASE in overall incidence is only apparent or is real, the finding of bilateral breast carcinoma in private practice is increasing. This may be due to the increased use of mammography and xeromammography. Management of the remaining breast in patients already successfully treated for breast cancer is most important in the follow-up care. The overall risk for development of a new primary malignant lesion in the opposite breast can be five times greater than in the general female population.[1] It has been stated that the longer the interval between mastectomies, the better the prognosis.[2] However, the diagnosis of bilateral simultaneous breast carcinoma, when the second primary lesion is nonpalpable (or occult), can result in a good prognosis. Early noninfiltrating cancer in the opposite breast can be detected by contralateral biopsy, as is done by Urban at the time of the initial mastectomy. An alternative to routine contralateral biopsy may be the use of xeromammography. Although routine contralateral biopsy may be lifesaving in detecting unsuspected carcinoma in the opposite breast, it is seldom practiced as it may be nonproductive in 83 to 86 percent of cases.[3] Therefore, the alternative of routine preoperative xeromammography is attractive.

Xeromammography has been reported as improving diagnostic accuracy when compared with conventional mammography because it produces an image of the breast in finer detail, giving great

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TABLE 1.—*Incidence of Bilateral Breast Carcinoma in Patients Treated for Primary Breast Carcinoma*

Source	*Bilateral/Primary*	*Percent*
Literature generally	....	1 - 14.0
Herrmann	31/418	7.4
Urban	70/488	14.3
Urban*	67/337	20.0
Spratt	14/704	2.0
Saint John's Hospital	34/1189	2.9

*Selected series-bilateral biopsy.

TABLE 2.—*Incidence of Bilateral Breast Carcinoma in Patients Treated for Primary Breast Carcinoma at Saint John's Hospital, 1950 Through 1974*

	Bilateral/Primary	*Percent*
1950-1968	18/916	2.0
1972*	2/106	1.9
1973	9/117	7.7
1974	8/74	10.8

*Xeromammography instituted October 1972.

TABLE 3.—*Incidence of Bilateral Breast Carcinoma and Use of Xeromammography at Saint John's Hospital*

Year	*No. Studies*	*Incidence (Percent)*
1972	120	1.9
1973	698	7.7
1974	1,053	10.8

promise as a method for the earlier diagnosis of breast cancer. In a 17-month program involving 4,183 xeromammographic studies, 133 malignant breast lesions were diagnosed and proven by biopsy findings. Fifty-two (or 39 percent) of these 133 were clinically unsuspected (nonpalpable). Of the 52 cases of occult cancer, malignancy had spread to the axillary lymph nodes in 22 percent. The other 81 palpable masses (cancer) had spread to the axillary lymph nodes in 51 percent of the patients.[4] Therefore, the use of xeromammography is an important tool to confirm a clinical impression of possible primary breast cancer in one or both breasts (simultaneous lesions) and to detect occult breast cancer, particularly in high risk categories.

Incidence of Bilateral Breast Carcinoma

The incidence of bilateral breast cancer has been expressed as ranging from approximately 1 to 14 percent or more in selected series. Table 1 shows an incidence of approximately 2.9 percent (34/1189) at Saint John's Hospital and Health Center in a 21 year period. This is comparable to rates of incidence found in other series that ended five years ago or more, indicating that mammography was apparently not a factor.[5] Close follow-up of personal cases by Herrmann resulted in a bilaterality incidence of 7.4 percent (31/418).[2] Urban's series with a higher bilaterality of 14.3 percent (70/448) seems dependent on careful follow-up in addition to contralateral random biopsy studies. In a selected group of patients in whom surgical operation was carried out at Memorial Hospital in New York—and in whom previous mastectomy or contralateral simultaneous biopsy had been done—there was a bilateral incidence of approximately 20 percent (67/337). In only 24 patients in Urban's series was conventional mammography carried out and the results were not particularly helpful in the detection of occult lesions.[3]

In more recent years with revival of standard or conventional mammography, the incidence of bilaterality noted at Saint John's Hospital (Table 2) in 1972 was still 1.9 percent (2/106). With the apparent increased use of xeromammography (instituted at this hospital in October of 1972), the 1973 incidence of bilateral carcinoma of the breast was 7.7 percent (9/117). With a lesser number of cases in 1974, an increased incidence of bilaterality (10.8 percent) has been noted.

Use of Mammography or Xeromammography as a Diagnostic Aid

The use of mammogram studies has doubled from an average of 44 cases per month before 1973 to an average of approximately 88 cases per month or a total of 1,053 in 1974 (Table 3). In the nine bilateral cases detected in 1973, xeromammography was used in five. Three of these cases were simultaneous—the second lesion was nonpalpable or occult in two of these. In four other patients—all with palpable breast masses—mammography was not done (mastectomy had been carried out previously in three cases and one was a case of simultaneous, bilateral masses). Of the eight instances of bilateral breast carcinoma detected in 1974, three were simultaneous bilateral lesions (two being unsuspected or occult).*

In one author's (CAK) personal series, the diagnosis of a nonpalpable or occult second lesion was made by mammography in every one of the most recent four consecutive cases. All of these four patients are alive 2 to 7⅔ years after a second mastectomy was carried out. In the one patient who died in this series, periodic mammography had not been done from the time of the

*Mammography statistics from the Department of Radiology at Saint John's Hospital and Health Center supplied courtesy of Conrad Frydenlund, MD.

initial mastectomy in 1957 to the time the patient returned in 1965 with a palpable mass in the remaining breast. She died 12 years after the first mastectomy was done and four years after the second mastectomy. In this patient no positive nodes were found at the time of either standard radical mastectomy. These observations and the increased incidence of bilateral breast carcinoma cases being detected in 1973 and 1974 would suggest the value of routine periodic xeromammography.

Treatment of Bilateral Breast Carcinoma

In Herrmann's personal series of 31 patients with bilateral breast carcinoma, bilateral radical mastectomies were done in all cases. In 28 of these 31 patients, carcinoma was nonsimultaneous, or asynchronous, and in only three was it simultaneous. A retrospective study of a so-called high risk group among his 418 patients failed to show the value of prophylactic removal of the remaining breast after mastectomy.[2] This finding is in agreement with the general and current consensus of other authors in regard to contralateral prophylactic mastectomy.

Urban has used radical mastectomy or extended radical mastectomy in patients with infiltrating carcinoma of the breast. In cases of noninfiltrating carcinoma he carries out radical mastectomy or modified radical mastectomy. He further states that since 1964 he routinely does random biopsy of the opposite breast. This consists of a generous biopsy of the upper outer quadrant as well as the mirror image area of the malignant lesion. He notes, "Approximately 20 percent of the breast parenchyma is removed in order to afford the pathologist an adequate specimen."[3] This was done in 73 percent of the available opposite breasts at the time of the initial mastectomy. It is usually not done in patients with advanced disease and poor prognosis or in elderly patients with poor survival expectancy.

In the authors' combined series of nine patients, 11 standard radical and 5 modified radical mastectomies were carried out. In one patient—an 8¼-year survivor—extended radical mastectomy had been done on the first side with findings of positive midaxillary nodes and negative internal mammary nodes. An occult lesion on the opposite side was treated by modified radical mastectomy four years later. There were no positive axillary nodes noted on this side and the patient is apparently free of disease. In another patient one breast lesion was treated with simple mastectomy (in a five-year survivor living with disease). Within the past year one other patient with bilateral simultaneous primary breast carcinoma was treated with bilateral incontinuity modified radical mastectomies.

Five-Year Survival Rates in Bilateral Breast Carcinoma

When carcinoma is detected simultaneously in both breasts, it does not denote a hopeless situation. There was a 75 percent (9/12) five-year survival rate (free of disease) in Urban's series of patients with simultaneous breast carcinoma. It is also of interest to note that in Herrmann's personal series there was a five-year survival rate (free of disease) of 57.9 percent (11/19) in bilateral breast carcinoma in contrast to an overall survival rate of his total series of 52.6 percent (220/418). Therefore, a careful follow-up with early diagnosis of the contralateral lesion appears at present to improve the survival rate in patients with bilateral breast carcinoma over that in patients with unilateral primary carcinoma.

In the authors' combined series, followed from one to eight years after the second mastectomy, the gross survival rate was 77.7 percent (7/9). Two of the survivors are living with disease, eight and five years after initial mastectomy. The age range of patients was from 41 to 73 years at the time bilateral breast carcinoma was diagnosed. One of the survivors living with disease is totally asymptomatic now, 8⅔ years and 6 years after mastectomies were done. In this same patient bilateral oophorectomy was done 5.8 years ago and bilateral adrenalectomy 3.7 years ago. Metastatic breast carcinoma was noted in both ovaries and adrenals. Findings on liver scan, carried out at six-month intervals, have changed from appearing to show several focal defects to "normal." The second patient living with disease is asymptomatic five years after mastectomies, now 3.5 years after bilateral oophorectomy and 3 years after bilateral adrenalectomy.

In comparing the above survival rates with the range of reported five-year survival rates for operable unilateral primary breast carcinoma, it would appear that the survival rate in properly treated bilateral breast carcinoma can be equal to or superior to that usually obtained with unilateral disease. This may be due to closer fol-

low-up and earlier diagnosis of the second lesion as previously stated. "Aggressive primary therapy is indicated when primary operable breast cancer is found simultaneously in both breasts."[3]

Conclusions

In our experience use of preoperative and periodic mammography has been helpful in detecting unsuspected occult carcinoma of the breast. Current xeromammography experience at Saint John's Hospital shows increased detection of bilateral breast carcinoma.

A sizable recent xeromammography series in the literature showed a 39 percent incidence of unsuspected or occult breast carcinoma. With the occult lesions there was a proven 22 percent axillary lymph node involvement. This would suggest that such occult lesions should be treated by at least a modified radical mastectomy of the second breast for potential cure, whether simultaneous or nonsimultaneous bilateral breast carcinoma.

Survival rates for bilateral breast carcinoma treated by standard radical or modified radical mastectomy appear to be equal to or superior to that usually obtained in unilateral disease. Present survival rates should improve, even in selected series, because of earlier detection of occult lesions with routine preoperative and periodic xeromammography.

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Unexplained Fever Following Intestinal Surgery

Certainly with temperature elevation (that is, temperature elevation beyond the first 48 hours), I think it is worthwhile to start a systematic investigation of the sources of fever. And for a patient who has had a wound, the wound is the first thing to consider as a cause for any temperature elevation. I have seen certain clostridial infections involving abdominal incision that caused fever the night following the operation. So, while we usually think of a wound infection as giving rise to temperature elevations about the third or fourth day, never dismiss the wound as the principle or perhaps prime source of a temperature elevation—even as soon as the night following operation. The point about patients with those clostridial infections is that they run their temperatures from that source early in the course of infection; and, especially concerning a clostridial wound infection, the sooner you make that diagnosis, the better your chances of successfully dealing with an otherwise highly lethal complication.

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Microsurgical Treatment of Hemifacial Spasm

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Five cases of idiopathic hemifacial spasm have been successfully treated by operative manipulation of arterial branches compressing the VIIth nerve in the posterior fossa. Terminology, clinical presentation, pathology and therapeutic approaches to hemifacial spasm are discussed. Hearing loss due to operatively induced vascular impairment of the inner ear, a complication in our first case, should be avoidable.

Our experience indicates that hemifacial spasm reflects mild chronic compression of the facial nerve. The proposed mechanism is transaxonal excitation between afferent and efferent fibers.

HEMIFACIAL SPASM (HS) is an uncommon affliction characterized by embarrassing and fatiguing facial twitching, usually cryptogenic but occasionally associated with subtentorial lesions, predominantly extra-axial vascular and neoplastic.[1,2] Because the cause is poorly understood, therapy has been empiric and unsatisfactory, and relief has been at the price of significant weakness of facial muscles.[3-5] Jannetta[6] has reported a series of eight patients in whom, with the aid of an operating microscope, he separated the facial nerve from a large branch of the anterior inferior cerebellar artery (AICA) in the cerebellopontine angle (CPA). His results in this initial study as well as in his subsequent[7-9] experience have been excellent.

Our series of five cases treated by Jannetta's microsurgical method confirms the efficacy of the operation and gives weight to the hypothesis that HS is often caused by mild chronic compression of the facial nerve.

Method and Case Reports

Since 1970 microsurgical vascular decompression of the intracranial facial nerve has been carried out in five of our patients with HS. All were women. Ages ranged from 44 to 66 years. The length of time from onset of symptoms to operation was 3 to 15 years. The patients have been followed up from three months to five years.

Surgical Technique

The operation is carried out under general anesthesia. Although Jannetta prefers to have the patient sitting, we have used a semiprone position. Through a short vertical incision medial to the mastoid process, a 3 cm craniectomy is used to expose the lateral and inferior angle of the posterior fossa. Under the operating microscope the responsible artery, usually a branch of the

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ABBREVIATIONS USED IN TEXT

AICA = anterior inferior cerebellar artery
CPA = cerebellopontine angle
HS = hemifacial spasm

posterior inferior cerebellar artery, is identified at the point where the facial nerve exits from the brainstem. The artery is teased away from the facial nerve, and a Teflon® sponge, fashioned to held the artery away from the junction of facial nerve and brainstem, is interposed.

Results

In the first patient (Case 1), an operation was carried out unsuccessfully one year before the procedure described in this report. At the original operation an arterial loop was found lying across the facial nerve midway between the brainstem and the internal auditory canal. At that time (six years ago) we did not recognize that the responsible artery compressed the facial nerve at its origin from the brainstem, and this *proximal* segment of the nerve was not exposed. Interposing a sponge between the arterial loop and the *distal* facial nerve failed to stop the patient's hemifacial spasm, and because of traumatic spasm induced in the internal auditory artery the patient became deaf. One year later the correct procedure was carried out with immediate disappearance of hemifacial spasm.

In all five patients there has been complete absence of hemifacial spasm for the duration of follow-up (three months to five years), and in all there has been normal function of the affected facial nerve. Except in Case 1, preoperative function of the VIIIth nerve has been retained in all patients. With no exceptions the postoperative course has been uncomplicated. Our results are summarized in Table 1.

Discussion

Hemifacial spasm has been called reflex facial spasm, facial hemispasm, chronic faciospasm, nictitating spasm and facial tic. Cushing coined the term "tic convulsif" to denote HS associated with tic douloureux. Nosik[10] classified isolated facial spasm into categories characterized by (a) cortical irritation, (b) facial nucleus involvement and (c) psychogenic origin. Wartenberg[11] further classified HS caused by nuclear firing as (a) cryptogenic, resulting from infectious or degenerative changes, (b) lesions of the peripheral facial nerve and (c) postparalytic following Bell's palsy. In addition HS may be classified as cryptogenic or idiopathic, and secondary. For the purposes of this paper only the former is considered to be true HS.

The clinical features are characteristic. The spasm usually begins in the periorbital muscles and is of spontaneous onset. Although mild at onset, insidious progression to involve most of the musculature of that side of the face is the rule. Spontaneous remission has been reported,[12] but is unusual. The affected side is equally likely to be the right or the left, although occasionally bilateral movements are observed. Should bilateral movements occur, one side does not move in synchrony with the other. A mixed tonic-clonic spasm is characteristic. Women are affected more often than men; HS is exceedingly rare in childhood. In adults the onset may occur at any age, although it begins most commonly between 30 and 50 years.

Paroxysms of facial spasm are precipitated by numerous factors including nervousness, fatigue and volitional facial movement. Movement often persists during sleep. Volitional effort fails to terminate the spasm. Findings on neurological examination are normal with the exception of the VIIth and VIIIth nerves unless the HS is associated with another pathologic condition. In 106 cases of cryptogenic HS reported from the Mayo Clinic by Ehni and Woltman,[13] facial weakness was present in 16 patients and hearing impairment on the side of the lesion in 14.

Contrast studies are not helpful except for the occasional discovery of a vascular abnormality in the region of the CPA[14] and assurance that the spasm is not secondary to one of the numerous pathological entities capable of producing sec-

TABLE 1.—*Results of Treatment for Hemifacial Spasm*

Case No.	*Age*	*Sex*	*Duration*	*Follow-up: No Recurrence*	*Complications*
1	47	Female	5 years	5 years	Deafness in left ear from previous operation
2	44	Female	3 years	1½ years	.....
3	61	Female	6 years	1 year	Mild hearing loss postoperatively; normal hearing restored
4	66	Female	4 years	6 months	.....
5	67	Female	15 years	3 months	.....

ondary facial spasm. Pathologic entities associated with HS include neoplasm and aneurysm in the CPA, basilar arachnoiditis,[1] intrinsic brainstem neoplasm,[2] purulent meningitis, tetanus, basal ganglion lesions, trigeminal neuralgia[15] and Paget's disease.[16] Virtually all of these entities cause additional neurologic abnormalities. Morbid pathology in HS is scarce, however, since the condition is benign.

Based on his observations in dealing with arterial loops compressing the Vth nerve in trigeminal neuralgia, Jannetta carried out operations and reported findings in eight cases of HS. He was successful in relieving facial spasm in all eight patients although in three hearing was lost in the ipsilateral ear and in one there was postoperative facial palsy. His series now numbers about 68 cases and he continues to advocate this approach.[9] There have been no additional cases of postoperative hearing loss since those that he described in his earlier series.

It appears certain that the basic pathologic lesion lies either at the nuclear level or distally.[17] Return of facial spasm due to regeneration of the interrupted VIIth nerve at the stylomastoid foramen may be prevented by anastomosis of the distal end with XI or XII. This would favor placement of the responsible lesion between the nucleus and stylomastoid foramen.[12] Gardner's attractive theory[12,18] that squeezing together nerve fibers results in reducing the thickness of myelin sheaths, leading to transaxonal short circuiting between afferent and efferent fibers, is supported by findings from both experimental[19,20] and clinical[21] observations.

Various nonspecific procedures have been applied to the treatment of HS. All of these are indirect approaches designed to differentially damage all or part of the facial nerve.[5] Although efficacious at times, alcohol injection, crushing or surgical interruption of the facial nerve results in cosmetically undesirable weakness of facial muscles. In addition, recurrence of the spasm is common.[3]

We believe that microdissection of arterial structures from the VIIth cranial nerve in the posterior fossa is a safe and effective method of dealing with cryptogenic HS and consider it the method of choice in dealing with this entity. Hearing loss due to operatively induced vascular impairment of the inner ear is a risk that the patient must accept, although this risk has been reduced with added experience.

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Medical
PROGRESS

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Progress in Peripheral Vascular Surgery

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ARTERIAL DISEASES rank among the most common illnesses of man and each year are responsible for an increasing number of deaths.[1-3] Arteriosclerosis, the most common of these arterial diseases, has been the subject of intensive study and many factors influencing its progress and its severity have been discovered and in some cases controlled. This massive research effort has not discovered the basic etiologic factors but it has shown important features which have been extremely useful in the management of these problems.

During the past two decades this tremendous surge of interest has generated a widespread clinical and experimental effort. Such efforts have been aided by the development of sophisticated angiographic techniques which permit the safe and precise study of arterial lesions. During the same period, improvements in vascular surgical techniques allowed immediate application of newly acquired concepts, and the ensuing successes captured the attention and imagination of many surgeons. In addition to these stimuli, governmental agencies have encouraged and supported research concerning the cause and treatment of arterial diseases.

The histologic features of arteriosclerosis, although well described, have not disclosed significant clues identifying exact etiological factors.[4] The varying susceptibility of different segments of the arterial tree to arteriosclerosis suggests that certain inherent features of these particular arteries render them more vulnerable. Deficient blood supply of the arterial wall has been implicated as a critical factor, therefore perhaps partly explaining the increased susceptibility of the terminal aorta, which lacks vasa vasorum. It has been suggested that the histologic features of arteriosclerosis are consistent with the process beginning as degeneration of smooth muscle cells in the wall. This may be an example of cells responding in a uniform fashion to injuries incurred as a result of different types of trauma.[4] It has also been shown that changes in blood lipids, both in content and quality, can exert undesirable influences upon the progression of arteriosclerotic lesions. Similarly, prolonged hypertension has been shown to accelerate the rate of progression of arteriosclerosis, suggesting that control of hypertension might slow this progression. Despite this widespread effort, understanding of the exact relationship of these factors has yet to be acquired.

As a result of these studies, certain basic concepts emerged and have been of great value in the management of arterial diseases. Many studies have centered on the morphological characteristics of arterial diseases and the pathophysiological changes produced by the altered hemodynamics. With the rapid development of vascular surgical techniques it quickly became apparent that surgical methods of treatment were available which might be applied directly toward the restoration of normal hemodynamics, despite ignorance of the basic cause. As DeBakey pointed out, the segmental nature of arteriosclerosis produces well localized disease with a relatively normal proximal and distal arterial bed and allows vascular

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surgeons to "leap over the etiological wall" and effectively treat these patients.[1] Several important morphological features have been delineated and among these the tendency of arteriosclerosis to be segmental rather than diffuse is very important.[5] Moreover, arteriosclerotic plaques in their formative stages are eccentrically located within the arterial wall and thus a portion of the artery may be spared. These features immediately suggested that bypass techniques might be feasible, and a relatively normal arterial wall opposite to the plaque might be used as a base for attaching grafts. Application of these concepts was directly responsible for the rapid progress evidenced by vascular surgery. Findings of further studies showed that in some cases the arteriosclerotic lesions tend to become stable late in the disease. Results of successful bypass operations might, therefore, be quite durable if methods could be developed to control the progression of the disease.

Findings in such morphological studies also suggest that arteriosclerosis in large arteries has two basic forms.[1,5] In one variety, the disease produces stenosis and subsequent occlusion, and in the other, ectasia and aneurysms. In the latter instance, the disease is not characterized solely by the proliferation of the subintimal plaque, but by destruction of the integrity of the wall, disruption of the elastic lamellae, and finally ectasia and aneurysmal changes. In accordance with those physical laws governing the relationship between diameter and tangential pressure, such aneurysms continue to increase in size. In some patients, associated distal occlusive lesions are also present, which shows that these diseases may coexist. Despite these problems, those principles applied to treating the occlusive lesion can also be successfully employed in the management of aneurysmal disease because it also tends to be segmental rather than diffuse. Such observations have shown the variation in the histological and pathological features of arteriosclerosis. Although the dissimilar nature of the changes in the arterial wall in stenotic and aneurysmal disease suggest different causes, this is uncertain because both lesions may be present in the same patient.

Altered hemodynamic patterns produced by proximal arterial stenoses are quite similar regardless of the basic cause. Consequently, in patients who have arteritis or arterial dysplasia as a cause of stenosis, symptoms may be seen quite similar to those caused by arteriosclerosis. Moreover, similar syndromes may exist in association with arterial trauma or emboli and therefore may also respond to appropriate surgical techniques. It is apparent that the restoration of normal hemodynamics is of immediate significance, while the treatment of the underlying cause may be classified as a concept of long-term management. Control of progression of these arterial diseases is, of course, very important if results of the initially successful surgical procedures are to have long-term durability. As alluded to previously, control of certain metabolic and hemodynamic features may retard the progression of arteriosclerosis. Unfortunately, those factors influencing the progression of arteritis and arterial dysplasia are not known.

Diagnostic Tests

Functional evaluation of the hemodynamic disturbances in these patients is important in assessing the need for surgical operation and subsequently evaluating the success obtained by surgical repair. It has long been recognized, and recently emphasized, that the most effective and reliable noninvasive technique in evaluating such cases is accomplished by obtaining a careful history and performing a thorough physical examination.[6] Although the diagnosis of vascular insufficiency is relatively straightforward, the concepts of pressure measurement originally introduced by Winsor in 1950 have been useful in assessing the arterial supply to the extremities.[7] Utilizing plethysmographic techniques Winsor measured pressures in arteries of the extremities and correlated these pressures with arteriosclerotic disease of varying degrees of severity. He suggested that measurements of segmental pressure in afflicted extremities might be useful in detecting areas of stenosis, and he also constructed indices for comparison of pressures between the brachial and tibial arteries. This concept has been employed by many other investigators and led to the development of instruments to be used for measuring distal arterial pressure.[8-10]

The Doppler ultrasonic flow detector has been extensively used in these measures. Continuing efforts by bioengineers have resulted in the production and marketing of small, relatively inexpensive ultrasonic flow detectors which have proven useful for these studies.[11] These techniques offer qualitative rather than quantitative data, but

have been especially helpful in the postoperative period, and in screening certain cases before arteriography.

A pulsed ultrasonic flow detector has recently been topographically synchronized to present oscilloscopic images which may be photographed, in this way affording some visualization of the contours of the vessel under examination. Similar to the results of radionuclide imaging, the contours are relatively hazy and not as well defined as those obtained with high grade arteriography, but nevertheless these are useful screening procedures. Ultrasound has also been employed in the form of echo ranging equipment in which techniques have been developed to delineate masses by comparing the differences in sound absorption and reflection of adjacent tissue. This B-mode scanning has been particularly useful to vascular surgeons in detecting the presence of arterial aneurysms, and in following their subsequent enlargement.[12] In many patients valuable information can be gained with these studies, and they may occasionally substitute for arteriography.

The introduction of bioengineering as an integral part of patient management has led to the development of other instruments which have proven useful in vascular laboratories. Measurements of electrical impedance of the extremities also offer information regarding the vascular supply. Sophisticated plethysmographic equipment utilizing mercury strain gauges may be used to study pulse wave forms and measure segmental pressures, and thereby assist in detection of zones of stenosis.[13,14] These pulse volume recorders can be employed during exercise, thereby permitting examination of changes when the muscles are active. Such data are valuable not only in the evaluation of the severity of the symptoms of the patient, but also in assessing the effectiveness and the durability of surgical reconstruction. These techniques have, for example, confirmed Edwards' concept that reductions in pulse pressure occur during exercise because of decreased distal arterial resistance combined with a proximal inflow block.[15]

Newer methods of measuring isotope clearance have also been of value in assessing ischemia of the lower extremity. The injection of sodium 124 or Xenon 133 into the muscle of the extremities and measurement of subsequent clearance permits a nuclear radiologist to indirectly assess the efficiency of blood flow in the small vessels.[16] These techniques may also indicate an increased rate of isotope clearance occurring during exercise. Potassium 43 may be used to detect and identify ischemic areas in striated muscle, complementing clearance studies.[17] Because of the expense and complexity of these tests they have mainly remained in the vascular research laboratories and have not been as useful in the clinical setting as some other methods.

Nuclear radiologists have developed techniques for radionuclide imaging of vessels. In these studies technetium 99 is injected and simultaneous scanning with a scintillation camera is done to produce an image that reflects the contours of the vessels.[18,19] Although these techniques lack the definition and accuracy of high quality angiograms, valuable information may be gained and direct puncture or catheterization of the diseased arteries may be avoided. In most cases angiograms will subsequently be required for a final decision, but such radionuclide imaging techniques may form the basis for a screening examination which in some patients may satisfactorily substitute for arteriography.

It has been amply shown by Linton, Edwards and others that arteriography is not always necessary for the diagnosis and management of patients with aortofemoral disease.[2] Nevertheless, high quality arteriograms are very useful and in some cases indispensable in making these judgments. Some studies are particularly helpful in planning vascular reconstructive procedures and in many cases postoperative arteriograms are essential. Following the early efforts in angiography by Brooks, Dos Santos and Moniz, these procedures have proven to be safe and very valuable.[20-22]

Translumbar aortography has been the most popular and useful technique for evaluation of the aortofemoral tree and continues to be used in many vascular centers. The extensive experience obtained with translumbar arteriography, and subsequently reported by Beall, DeBakey, Crawford and colleagues, outlined the basic principles of the procedure, and proved its safety and effectiveness.[23] Complete visualization of the infrarenal aorta, iliac and femoral-popliteal systems is essential in most cases, and can be readily obtained with techniques developed many years ago. The safety of a properly conducted translumbar

arteriogram has been repeatedly shown and the information obtained from these studies is very useful.

The Seldinger technique of percutaneous catheterization of major vessels added another dimension to arteriographic studies and continues to gain in popularity.[24] These techniques offer new versatility and allow the vascular radiologist through a single arterial entry to examine many portions of the arterial tree. The development of flexible and flow directed catheters and improvements in x-ray equipment have permitted catheterization and visualization of even small splanchnic arteries. Although at present quantitative data are not obtained, qualitative evaluation of flow patterns can be ascertained and are useful in assessing the severity of arterial lesions. The safety of these carefully conducted studies allows repetitive examination to be done and has permitted a broadening of the indications for arteriography.

The administration of microspheres and vasoactive agents and the visual examination of the effect upon distal vessels may offer valuable information as to the functional integrity of smaller vascular beds. Immediate visualization of the effects of certain drugs promises to be of use in the development of new therapeutic modalities to control and regulate the distal circulation. Specific efforts to treat congenital arteriovenous fistulae by direct embolization using these catheters has been successful in a number of cases and promises an increasing range of applicability.[25]

Arteriography either by direct puncture or by percutaneous catheter techniques is indispensable in the diagnosis and management of occlusive disease of the visceral and cerebral vessels.[26-28] Sophisticated biplane studies are often necessary to expose small ulcerative plaques and to correctly identify obstructive lesions. The safety of these techniques has been repeatedly shown and several series reflect thousands of arteriograms carried out with low mortality and morbidity.[29,30] Following the introduction of newer and better contrast media for arterial arteriography, previously seen complications of renal failure and spinal cord damage became extremely rare. It is now apparent that with the current techniques and proper precautions these complications no longer pose a significant threat.

Arterial entry of any type carries with it the possibility of damage to the arterial wall which may cause localized thrombosis and in some cases embolization. This is more likely to occur in percutaneous catheter studies, in which the catheter may become ensheathed with clot during a prolonged procedure, and as the catheter is removed the thrombus is stripped off and remains within the vessel. This is an unusual occurrence as shown in Lang's collected series of more than 11,000 arterial entries, with 81 major and 325 minor complications, and a total of four deaths.[29] This is also reflected in Mortenson's series, which again shows the relative safety of these procedures.[30] From the national cooperative study on cerebral vascular disease, in which more than 4,700 studies of cerebral vessels were undertaken, serious complications occurred in only 1.2 percent of the patients.[28] More recent data indicate that cerebral vascular arteriography under proper conditions carries a risk of inducing a serious neurological deficit or of producing a lethal complication in less than 0.1 percent of the studies.[31] Vascular radiology has emerged as a growing specialty because of these many refinements in safety and technique and the indications for its use have increased at a rapid rate.

The recent development of a computer controlled and analyzed method of x-ray tomography promises to change many diagnostic techniques.[32] Computer tomography basically consists of computer analysis of the amount of x-ray absorption by various tissues. The beams are precisely passed through the area to be examined; the amount of irradiation absorbed is dependent upon the type of intervening tissue or substances. Differentiation between ischemic and hemorrhagic infarcts may be possible with this technique. Blood clot can be easily identified, and therefore intracranial lesions may be better exposed with this test than other noninvasive methods. The management of cerebrovascular insufficiency is certain to be significantly influenced by this innovative technique.

Arterial Grafts

Since the introduction of the plastic graft by Voorhees and his associates in 1952, arterial prosthetic implants have undergone many changes, but it is obvious that the ideal substitute has not been discovered.[33] Currently the most commonly used grafts are constructed of knitted Dacron® yarn, but in some instances knitted and woven Teflon® are also employed. The porosity is adjusted to permit the ingrowth of fibroblasts in an attempt to support formation of a neo-intima. It

is clear, however, that the new lining of these grafts usually consists of impacted fibrin and in most cases is not a living cellular layer. Some ingrowth over the suture lines of each individual graft may occur, but complete healing of the graft is not often obtained. Nevertheless, Dacron prosthetic implants have been extremely useful and the experience reported from many vascular services has suggested that these are the most acceptable of the available plastic grafts.[34]

Recent experiences, however, warn that the long-term behavior of these grafts may be less reliable than originally thought.[35-37] Aneurysm formation, loss of tensile strength and fiber breakage have appeared and such failures, although quite rare, suggest manufacturing defects or biodegradation. In other instances mechanical trauma during processing or implantation has been thought to cause late failure. Of more etiological importance may be the techniques in which chemical shrinkage of the knitted graft is induced to increase the porosity. These methods may cause a significant loss of tensile strength, and when utilized to produce the higher degree of porosity thought to be desirable, stiffness and brittleness of the Dacron fibers may supervene. Such changes in the graft would appear to seriously compromise the long-term integrity of these implants. Edwards, the originator of the Teflon graft, has continued to suggest that it may be less susceptible to these influences.[38] These reports of failure of Dacron grafts lend credence to this suggestion, and strongly indicate that a reappraisal of the characteristics of the currently employed arterial implants be undertaken.

Sauvage has described the construction and utilization of a Dacron filamentous graft that supports living pseudointima consisting of fibroblasts.[39] The basic aim underlying development of this graft was to provide for the migration of fibroblasts a trellis along which cells could be directed toward the lumen of the arterial prosthetic implant; there they would form and support a living surface which would be relatively electronegative and less favorable to late thrombosis. The long-term behavior of this graft should be more reliable if such a lining can consistently be induced, and preliminary reports suggest that this may be possible. In addition, the healed external capsule may offer support to the long-term integrity of the wall of these Dacron grafts. Wesolowski, Sauvage and many others continue the intensive investigation into the acquisition of artificial prosthetic materials which are more acceptable for arterial implants.[40,41]

Recent advances in the development of plastics have led to the suggestion that expanded polytetrafluroethylene may be molded into an arterial implant which embodies many of the desirable characteristics alluded to in the previous section.[40] These grafts also have a filamentous design to assist in the orientation and migration of fibroblasts, and moreover, seem to lack the intense thrombogenicity seen in Dacron grafts. Early reports from vascular centers studying these newer materials suggest that even small grafts may be utilized, a characteristic not shared by Dacron and Teflon, and therefore they may be eventually useful as aortocoronary bypass grafts when suitable saphenous veins are not available. Enthusiastic reports of early successes in the experimental laboratories and in a few instances in patients have stimulated an intensive investigation. If these early reports prove to be well founded a new era in arterial grafting may be opened.

Initial efforts to secure other grafts to be utilized in those patients in whom autogenous tissue was not available were relatively unsuccessful because of lack of tensile strength and thrombotic tendencies of the finished products. In many cases collagen tubes were fabricated, following the lead of Schilling, Sparks and others.[42,43] Dies were placed in the subcutaneous tissues to incite and direct the growth of an autogenous collagen tube that might be used as an arterial implant. These procedures have been useful in certain cases but their versatility is limited by the fact that in many instances the relative urgency of the procedure does not allow time for growth and harvest of an autogenous collagen tube.

Because of these reasons Rosenberg, Keshishian and others looked into the possibility of acquiring heterografts and treating them to reduce their antigenicity and to increase their tensile strength.[44-46] The current preparation, bovine carotid artery, is satisfactory in most cases. The artery is first digested by ficin, leaving a residual collagen tube, which is tanned with dialdehyde starch to increase its tensile strength. This graft has been very useful in many cases, especially in those patients in whom there was not a suitable saphenous vein. It carries the obvious advantage

of not requiring pre-clotting and appears less susceptible to the dense fibrous incapsulation and rigidity which unfavorably influences the long-term behavior of plastic prosthetic implants. These bovine heterografts have also been used in the construction of arterial-venous fistulae for hemodialysis and intravenous hyperalimentation. Such heterografts tend to retain their integrity despite numerous punctures. In certain cases localized aneurysms have occurred but some of these have been successfully resected and graft segments interposed to restore continuity and thus salvage the conduit. Studies in these patients have shown a low order of graft antigenicity. These preliminary data suggest that bovine grafts may be more satisfactory than plastic arterial substitutes in the lower extremities.

Vein Grafts

One of the major factors limiting the long-term success of saphenous vein bypass grafts has been primary vein failure. Early studies of aortocoronary vein grafts indicated a low but significant attrition rate due to an intense fibrosis causing thrombosis. These problems have not been common in vein grafts placed in the aortorenal, femoral-popliteal or femoral-tibial position, but localized areas of damage and subsequent stenosis or thrombosis have been described. Reports by Szilagyi, Stanley, Dean and their associates have shown that injuries incurred at the time of harvest of the saphenous vein may be responsible for many of these untoward effects.[47-49] Ischemia and hypoxia may also damage the vein and predispose it to fibrosis, stenosis and subsequent thrombosis. In addition, injury produced by rough handling may produce discrete lesions in the vein which ultimately lead to stenosis.[50] There is highly persuasive evidence that the thrombosis may occasionally begin on the distal side of the valve cusp where there is early aggregation of platelets and fibrin deposition.

In many cases harvesting of the autogenous vein has been left to the more junior person on the surgical team and it was inevitable that proper handling of the vein might not be achieved in all cases. Recent studies suggest that certain precautions should be taken when removing the veins for use as arterial implants; these include minimizing the warm ischemia time and avoiding overdistension and the use of crushing clamps—which may cause intimal damage.[50] The vein should be left in its natural bed until just before use, keeping the ischemia time to a minimum. If there is delay before insertion the vein should be handled as an allotransplanted organ and protected by hypothermic perfusion with balanced crystalloid or colloid solutions. It has been suggested that perfusion of the vein may best be accomplished with a cold heparinized autogenous solution of whole blood, particularly if it is necessary to remove and store the vein for even short periods.[48] These precautions cannot be overemphasized since vein grafts are being inserted with increasing frequency in almost every major hospital in the United States.

Studies investigating the late behavior of saphenous vein autografts have revealed a curious phenomenon. Some 15 to 20 percent of saphenous vein aortorenal grafts tend to increase in diameter, and in 4 to 6 percent of cases true aneurysms have occurred. Stanley, Dean and their associates have suggested that this may be a reflection of the increased velocity of blood flow to the kidney.[48,49] Lack of surrounding tissue support has been indicted, but this is also a feature of aortocoronary grafts, and these tend to become stenotic rather than aneurysmal. There are currently in progress intensive and urgent investigative efforts directed toward elucidating these phenomena. Serial angiographic studies are being obtained in order to carefully follow these changes in venous autografts. It is apparent that a considerable amount of work is yet to be done if such untoward late effects are to be removed and long-term function of these grafts improved.

Adjunctive Methods

Heparin has been extremely useful in many phases of vascular surgery, but specific indications and methods of administration have repeatedly changed during the past decade.[51] Heparin is obtained from beef lung or porcine gut and its potency is somewhat stronger in the latter preparation. It has been shown to exert its anticoagulant effect by inhibiting factor seven and factor nine, and also acting as an antithrombin. In higher doses it interferes with the thrombin-platelet interaction and the subsequent release reaction. It apparently has a biphasic action and in low doses does not change platelet stickiness, but in the high ranges may inhibit platelet aggregation.[52] It is an anti-inflammatory and an anti-aldosterone agent, and also has the ability to inhibit serotonin release and to induce clearing of blood lipids.[53] Recent studies strongly suggest that

the most favorable mode of heparin administration is by the continuous intravenous route utilizing a pump for steady infusion.[54] This technique is apparently safer and the therapeutic effects may be obtained with a lower overall dose. Tighter control is achieved and thus the more significant bleeding complications occur less commonly. Intermittent intravenous injection is also useful in certain cases, but apparently is accompanied by slightly more common side effects.[54]

There is persuasive evidence that the administration of smaller amounts of heparin, 5,000 units administered every 8 to 12 hours, may reduce the incidence of deep vein thrombosis and subsequent thromboembolic phenomena, particularly in high risk patients.[55] This appears to be the result of potentiation of factor Xa inhibitor, a natural anticlotting agent. Other studies dispute the efficacy of heparin in these situations. It is clear that the effectiveness of heparin in such patients is not yet decided.

Heparin is clearly of great value in vascular surgery, and this is especially true in the initial management of patients with arterial emboli, and during operations on renal and cerebral arteries. Most surgeons also utilize heparin during operative procedures on other parts of the arterial tree, especially femoral-popliteal, tibial and occasionally aortoiliac and aortofemoral vessels. Postoperative anticoagulation is rarely employed in most vascular clinics because heparin has been shown to occasionally induce serious bleeding and is associated with a higher incidence of wound infections. Moreover, there is little evidence that heparin will salvage a poor vascular repair, and most vascular surgeons believe that a satisfactory arterial reconstruction does not require postoperative anticoagulation.

It has long been recognized that plasminogen activator is present in greater concentration in the walls of veins and pulmonary arteries than in the walls of systemic arteries, especially larger and less muscular ones. The natural history of clots in the venous and pulmonary system has been one of spontaneous lysis and recanalization.[56] This is an unusual occurrence in systemic arteries and is thought to be due to this relative lack of plasminogen activator in these vessels, but perhaps is also influenced by the progressive stenosis of arterioclerosis. Because of this disparity in normal fibrinolysis, there have been many efforts to initiate clot lysis by the administration of other activators. This has largely centered around the use of streptokinase and more recently urokinase. Initially these activators were difficult to use because of their antigenicity, cost and lack of standardization. Early preparations were unsatisfactory but interest continued in the experimental laboratories. With recent manufacturing improvements, a preparation was developed which could safely be employed in a controlled patient study. The study was initially concerned with pulmonary emboli, and in a multidisciplined cooperative protocol lysis was achieved by a carefully regulated course of intravenous streptokinase.[56] Findings on pulmonary angiographic studies indicated that administration of this activator did indeed shorten the time required for clot lysis, but mortality analysis showed that there was no significant change in patient survival. Urokinase, apparently safer but more expensive, has not been available in sufficient quantities to assess its efficacy, although numerous studies are currently in progress.

Because of the success achieved in hastening lysis of clots in the pulmonary circulation it has been suggested that streptokinase might be useful in the management of arterial emboli and thrombosis.[57] Unfortunately establishment of satisfactory protocols for its evaluation is difficult because in many of the patients concerned, thrombosis may ensue in the immediate postoperative period when it is hazardous to administer a plasminogen activator. This is particularly true following major vascular procedures. On the other hand, those patients in whom thromboembolic phenomena and threatened viability of an extremity are present are not suitable candidates for the administration of an agent whose effect is necessarily delayed. In many cases viability of the extremities will be measured in hours and direct intervention will be required if tissue loss is to be prevented. Despite the initial enthusiasm, activation of the endogenous fibrinolytic system in the management of thromboembolic disease has not been as useful as hoped. In previous studies the activator was administered directly into the artery in an attempt to localize its effect and intensify its ability to induce clot lysis. Perhaps the newer arterial catheterization techniques may be mobilized in this area, and when joined with the administration of plasminogen activator, procedures may be developed which would permit clot lysis in patients with acute thromboembolic phenomena.

Adjunctive Methods—Platelets

It has been established, especially in the cerebral circulation, that platelet emboli originating in arteriosclerotic ulcerative plaques are an important cause of distal arterial obstruction.[58] There is also persuasive evidence that adherence of platelets to endothelium results in endothelial damage which may be related to subsequent arterial thrombosis. Methods of inhibiting the aggregation of platelets are under intensive study, and it has been shown that certain agents interfere with this phenomenon. In platelet aggregation two basic reactions are involved: the stimulus presented by exposure of platelets to collagen and the aggregating effect of adenosine diphosphate—released as a result of the initial surface reaction. Certain groups of chemicals have been shown to inhibit these reactions and are generally divided into three types. Tricyclic compounds include some antihistamines and tranquilizers, but the mode of action is not clear. The pyrimidopyrimidine compounds act by interfering with the adenosine diphosphate (ADP)-induced platelet aggregation. The most commonly employed representative of this group is dipyridimole. The third group of drugs, the nonsteroidal anti-inflammatory agents, include sulfinpyrazone and aspirin.[59]

Aspirin is considered useful in blocking the surface release reaction of platelets and may also interfere with secondary ADP-induced aggregation. It also inhibits epinephrine-induced release of ADP; collagen and ADP-induced activation of platelet factor IX. It does not impair the response to thrombin. These drugs may therefore be initially useful in the treatment of arterial diseases which are accompanied by platelet emboli. They may also be of value in inhibiting the aggregation of platelets in the immediate postoperative period after vascular reconstruction. Their prophylactic effect continues to be disputed both in arterial and venous diseases because of conflicting reports, reflecting in many cases differences in protocols and study techniques.[60] Cooperative studies are currently in progress to ascertain the effectiveness and mechanisms of action of these agents. Preliminary reports by Salzman, Silver, Evans and others strongly suggest that these agents will be extremely useful both therapeutically and prophylactically in vascular surgery.[60] At the present time, however, the exact indications for use and modes of action remain unclear.

Aortoiliofemoral Occlusive Disease

During the past two decades a tremendous amount of experience in the management of occlusive aortofemoral disease has been accumulated. A unique opportunity to construct a profile of vascular occlusive disease has been offered vascular surgeons. This is largely the result of the opportunity to correlate symptomatology, physical findings and angiographic illustration of the lesions with the direct operative examination of morphologic and histopathologic characteristics.

Arteriosclerotic lesions of the vessels supplying the lower extremities tend to be distributed in such a fashion as to spontaneously separate into three groups.[1,5] The first, aortoiliac disease, is characterized by primary involvement of the terminal aorta, the common iliac and hypogastric arteries. The disease usually tends to end in the proximal 1 or 2 cm of the external iliac arteries. Patients with this "pure" form of aortoiliac occlusive disease are younger, tend to have less widespread and less severe arterial disease and have milder symptoms.

More commonly the distribution is aortofemoral and involves the entire infrarenal aorta and the iliac system, and plaques are also found in the common femoral, the profunda femoris and the superficial femoral arteries. Segmental accentuation is present but less distinct in these patients. As expected they are somewhat older and have more diffuse arterial disease. These people also have more severe associated symptoms, especially from lesions present in the coronary, renal and cerebral arteries. Associated hypertension is present in almost half of these patients, myocardial disease in a third and cerebrovascular and renal disease in approximately 10 and 15 percent respectively.

In the third variety the major plaques are in the femoral, popliteal and tibial system. In these patients the lesions are most severe in the superficial femoral artery as it traverses the adductor canal, but also involve the popliteal, especially in its mid and terminal portions. The orifices of the tibial arteries are often stenotic. These patients tend to be somewhat younger than those encountered in the aortofemoral group, and often have diabetes or lipid disorders or both. Of course, in its more severe forms, the separation is less distinct. One may, therefore, expect to encounter combinations in many patients. It has been shown, however, that in only 10 to 15 percent of patients having

successful aortofemoral repair will femoral-popliteal reconstruction be required subsequently.[61,62]

The clinical syndromes which eventuate as a result of arteriosclerotic lesions of the aortofemoral system can be roughly divided according to their severity. Those patients with a "pure" form of aortoiliac stenosis and with the milder forms of aortofemoral or femoral-popliteal lesions often present with mild ischemia, characterized by claudication. This claudication may be slowly progressive and the severity of the ischemia may increase, but in many instances it remains relatively stable for long periods. In only a small proportion of patients is amputation eventually necessary. In its most severe form, however, the ischemia produces disturbances in tissue nutrition which eventuate in ischemic rest pain, and if untreated, gangrene. The importance of assessing the functional significance of these lesions cannot be overemphasized since they often yield to established vascular procedures. Nevertheless, the eventual outcome in these patients is more often determined by the severity of associated arterial disease, particularly when coronary and cerebral vessels are involved.

The operative management of occlusive disease of the aortofemoral tree basically employs one of three techniques, or various combinations. Thromboendarterectomy, employing autogenous tissue and thus excluding the need for graft implantation is appealing and has been successfully used in many cases. This technique unfortunately cannot be applied to all cases, and is usually limited to those patients who have relatively localized disease of the aortoiliac tree. Arterial aneurysms or vessels with severe calcification involving the entire wall of the artery are not suitable for this technique. Disruption of the artery and early thrombosis are often seen in these cases. Other problems are encountered with long endarterectomies of the superficial femoral and popliteal arteries, which may be followed by an intense fibrotic reaction. Accumulated experience has indicated that aortoiliac endarterectomy is a useful technique, but when the disease is more diffuse and involves the entire aortofemoral tree, bypass grafting is easier and just as successful. Careful analyses presented by Szilagyi, Gaspard, Stoney and other workers indicate that little difference can be shown in the success and durability of aortofemoral grafts in comparison with aortofemoral endarterectomy.[61-64]

Although the morbidity following these procedures is approximately 20 percent, mortality rates of 2 to 4 percent are regularly reported. Five- and ten-year studies of patients having undergone aortofemoral reconstruction show the operation to be remarkably durable, considering the disease encountered in some patients. Continued patency rates of these repairs in 70 to 80 percent of patients have been repeatedly shown.[65,66] Those patients with disease limited to the aortoiliac segment regularly exhibit five-year patency rates in excess of 85 percent, but as expected the operations are less successful in those patients with aortofemoral disease and especially if there are associated femoral-popliteal occlusive lesions.

Femoral-Popliteal and Tibial Disease

In some patients with vascular insufficiency of the lower extremities the predominant arteriosclerotic lesions will be found in the femoral, popliteal and tibial vessels. This is particularly likely to occur in patients with diabetes mellitus, thromboangitis obliterans and various lipid disorders. In addition, there is a group of relatively young adults in the third and fourth decades of life who appear to have an increased incidence of femoral-popliteal arterial disease, but in whom no specific causes have been found.[67]

Certain basic patterns of involvement are frequently encountered and it has been repeatedly observed that the superficial femoral artery as it passes through the adductor canal is extremely susceptible to stenosis and occlusion. Haimovici observed and reported on the patterns of arteriosclerotic involvement of lesions in the lower extremity and these data offer useful guidelines for study of this disease.[68] Subsequent reports by Morton and co-workers characterized the patterns of tibial disease associated with arteriosclerotic involvement of the popliteal artery, and related these changes to the possibilities of successful reconstruction.[69] Reports by Linton and Darling, and Crawford and his colleagues confirmed the pattern of involvement which characteristically includes occlusion of the superficial femoral artery and reconstitution of the distal popliteal and tibial vessels.[67,70]

The diagnosis of disease of the femoral-popliteal and tibial vessels is relatively simple in most cases because direct examination of the superficially located arteries is possible. Plaques can

often be palpated in the femoral vessels and occasionally in the anterior and posterior tibial arteries. It is relatively simple to detect diminished pulses, bruits, and zones of stenosis and obstruction. Measurements of distal pressure and flow as originally conceived by Winsor may be of value in the assessment of these problems, but in most cases complete angiographic evaluation is necessary in order to properly plan the method of vascular repair.

The indications for operation in patients with femoral-popliteal disease and vascular insufficiency of the lower extremities must be carefully evaluated and stringently applied. It is a rare happening in a patient with claudication caused by aortofemoral disease for loss of an extremity to occur as a complication of surgical operation, but this is more of a threat in femoral-popliteal and femoral-tibial reconstructive efforts.[71] The initial determination of the need for operation must be balanced against the hazard attending the procedure. It is apparent that in those patients with diffuse tibial disease and a reduced outflow tract the likelihood of technical success diminishes and the risk to the extremity increases.[72] Most surgeons limit femoral-popliteal and femoral-tibial bypasses to those patients in whom there are symptoms of vascular insufficiency that are so severe as to interfere with normal day-to-day activity and preclude their being gainfully employed. In patients in whom rest pain and other signs of severe ischemia are present, surgical repair is necessary in order to assure viability of the extremity. It is apparent, however, that in those instances in which technical repair cannot be successfully accomplished, changes in cardiac function, increased metabolic demands placed upon the operated extremity and the interruption of vital collateral channels may precipitate loss of the limb. In these patients, therefore, the indications for operation should be very strong. This is especially true if it is feared that satisfactory conclusion of the operation may not be achieved because of inherent technical difficulties.[72]

In the usual operation the reversed saphenous vein is placed from the common femoral to an appropriate position in the mid or distal popliteal artery and occasionally to one of the tibial arteries.[73] These procedures are accompanied by common and profunda femoral thromboendarterectomy if these arteries are significantly compromised by arteriosclerotic plaques. In some cases composite grafts may be constructed of a combination of saphenous vein and tube plastic grafts, or sections of bovine heterograft. This may be necessary in those instances in which the saphenous vein is of insufficient length and other autogenous veins, such as the cephalic vein, are not available. The studies presented by Mannick and others suggest that the distal anastomosis may on occasion be made to an isolated popliteal artery, without patent tibial arteries, and yet success be achieved in up to 50 percent of patients.[74] Most surgeons, however, would favor in this situation extending the graft distally and attaching it end-to-side to a tibial artery, thus bypassing all the proximal lesions.

The data developed by Mannick also showed that after bypass grafting an additional increase in blood flow could be obtained by adding a lumbar sympathectomy.[75] It is apparent, however, that in and of itself sympathectomy is of much less value than an adequate reconstruction, and if sufficient flow through the graft can be obtained initial patency in nine out of ten patients has been reported. In those patients with a satisfactory outflow tract (that is, two or three patent tibial vessels), five-year patency rates of 80 percent have been reported. Several series at ten years report continued patency of up to two thirds of the grafts. The operative mortality is usually low and such long-term successes have generated a considerable amount of enthusiasm for these operations. There are dissenting reports, however, by Stoney and Martin and their colleagues.[72,76] These workers have suggested that the attrition from associated arteriosclerotic vascular disease is of such magnitude that the ultimate limb salvage in the patients with severe ischemia is quite low, 25 to 35 percent at five years. These somber reports suggest that a reappraisal of the usefulness of this operation be undertaken. It is difficult to reconcile these conflicting reports from established vascular clinics, each with a great deal of experience.

The debate as to the effectiveness of this procedure is further compounded by the studies of Garrett, and Tyson and Reichle and their associates.[77-79] These workers have shown that femoral-tibial bypass grafts utilizing the reversed saphenous vein are quite effective in patients in whom femoral-popliteal grafts were not feasible. Reports by these surgeons suggest that construc-

tion of these bypasses may be somewhat more difficult but initial success rates may be achieved in approximately 50 percent of patients. The long-term behavior of the grafts is quite good, and five-year patency rates of 75 percent have been reported. Limb salvage in many cases has been dramatic and in most patients the operation is proposed only as an attempt for limb salvage.

There is less enthusiasm for thromboendarterectomy of the superficial femoral and popliteal arteries, although in some cases localized plaques may be removed by this technique. Findings in numerous studies done in the last decade have shown that although initial patency following femoral endarterectomy is quite high, the procedure may not be as durable as vein grafting. These techniques may be required in some patients when autogenous veins are not available, but in most cases the majority of vascular surgeons prefer to utilize knitted Dacron or bovine heterografts as a femoral-popliteal bypass graft rather than carry out a long endarterectomy. Crawford has reported that in those cases in which 8 mm knitted Dacron grafts are inserted in the femoral-popliteal position patency rates quite similar to those reported with reversed saphenous vein can be achieved.[80] For plastic grafts to remain patent a better outflow tract is required and it appears clear that these prostheses are less desirable and although initially successful cannot be expected to be as useful as the reversed saphenous vein.

Bovine heterografts are favored by many vascular surgeons.[44] They have the obvious advantages of not requiring preclotting, and they are pliable and easier to handle than plastic grafts. The available sizes are limited, but 6 or 7 mm grafts are very useful in femoral-popliteal operations. The long-term behavior of these grafts, like plastic implants, appears less satisfactory than that obtained with vein grafts. Their major utility would seem to be in those patients for whom a satisfactory autogenous vein is not available.

Abdominal Aortic Aneurysms

Arterial aneurysms are common manifestations of generalized arteriosclerosis. It is estimated that 2 to 4 percent of the general population over 25 years of age have abdominal aortic aneurysms, but they usually occur in people in the sixth or seventh decade of life. Males outnumber females by a nine to one ratio.[81] In most instances the abdominal aortic aneurysms are fusiform and in 98 percent of cases are distal to the renal arteries. Other causes of aneurysms include syphilis, trauma, sepsis and inherited arterial disorders, such as Marfan's syndrome. Segmental accentuation, as seen in the occlusive forms of arteriosclerosis, is also present, but less pronounced in patients with arterial aneurysms. There is a great tendency for concomitant involvement of the iliac arteries when an abdominal aortic aneurysm exists and it is not rare to also encounter in the same patient aneurysms of the common femoral and popliteal arteries. When these combinations do occur, bilaterality is frequent and may further complicate the management of these cases.

The natural history of abdominal aortic aneurysms has been elucidated by many studies. Initial reports by Estes and Wright suggested that most of these lesions inexorably increased in size, and approximately 40 percent eventually ruptured.[82,83] These authors further stated that the five-year survival of untreated patients with abdominal aortic aneurysms greater than 6 cm in diameter was less than 10 percent. These initial studies were not accompanied by satisfactory controls, but Szilagyi and co-workers have examined the natural history of these lesions utilizing actuarial protocols and life table methods.[84] These studies contained a matched series of patients from which two groups, one treated surgically and one not treated surgically were prospectively evaluated in regard to morbidity, rupture and survival. These data confirmed the initial impression that aneurysms greater than 6 cm in size were more dangerous than smaller ones, although rupture was not confined to large aneurysms. It has therefore been established that over 35 percent of aneurysms greater than 6 cm in diameter rupture and cause an alarmingly high morbidity and mortality. In fact, of 280 patients in whom resection was not undertaken because of various nonmedical reasons the five-year survival rate was only 6 percent, while in over 400 comparable patients who had elective abdominal aneurysmectomy the five-year survival was 47 percent, including operative mortality. These studies also showed that the rupture rate was significantly higher in patients with sustained hypertension.[84,85]

Although initially thought to be infrequent, recent reports have suggested that distal embolization may occur in up to a third of the patients

with aortic aneurysms.[86] Such epidemiologic studies clearly strengthen the rationale for excision of large aneurysms in patients in whom the risk of surgical operation is not prohibitive and the outlook for continued survival is reasonable.[87] This is especially important if the patients have sustained hypertension.

The diagnosis of peripheral arterial aneurysms is made on physical examination in most cases, but in some instances may require arteriography for confirmation. Newer techniques employing echo-ranging equipment are useful in determining size and rate of growth of these aneurysms. In fact, the B-mode ultrasonic scanning has been shown to accurately measure aneurysm size in many patients.[12] Findings on plain x-ray films may indicate the presence of calcification and correlate with clinical findings, but in some instances these studies fail to show the aneurysm. Because of the occasional involvement of associated visceral arteries, particularly renal and mesenteric, aortography is being used more often. Many surgeons believe that most cases should be angiographically examined in order to plan the operative management, and to assess the visceral and distal circulation before surgical operation. Despite the validity of these indications, most abdominal aneurysms are diagnosed clinically, and usually resected without the benefit of angiography.

The operative management embodies those same principles that are employed in the management of occlusive disease of the aortofemoral tree. Early efforts to induce thrombosis by wiring and ligation or to control expansion by aneurysmorrhaphy have largely been supplanted by resection and graft replacement. By far the most common procedure currently employed in the surgical management of abdominal aortic aneurysms is resection and graft replacement. In most cases the aneurysms are isolated and after removal of a portion of the anterior wall of the aneurysm the graft is sewn to the aorta just distal to the renal arteries. The distal limbs of the graft are attached beyond the disease to either the iliac or the femoral vessels.

In the elective situation these procedures are highly effective and mortality rates as low as 4 percent have been reported from centers experienced in surgical management of aneurysms.[12,81,84] In contrast are those patients for whom operations must be undertaken in the face of an acute rupture. Mortality rates in excess of 50 percent are almost always encountered.

Sepsis

Of the complications which may occur following prosthetic grafting, one of the most distressing is that of infection of the anastomosis. Infection of the shaft of the prosthetic implant may occasionally yield to appropriate antimicrobial therapy and drainage, but as shown by Szilagyi, Smith, Elliott and associates, postoperative infections which involve the anastomotic line or the neointima are rarely successfully managed without removal of the prosthetic implant.[88,89] These complications are extremely hazardous both to the patient's life and to the survival of the afflicted extremities. Graft infections are fortunately very rare and several large clinics have reported an incidence of 1½ to 3 percent. Once anastomotic infection is present, false aneurysm, thrombosis and bleeding are the rule, and if early intervention is not successful loss of the limb or a fatal outcome can be expected.

The concepts of establishing remote bypasses through clean tissue planes before removal of the infected prosthetic implant were originally promoted by Blaisdell and Hall, and Shaw and Baue.[90,91] The importance of these principles cannot be overemphasized. Axillary-femoral, femoral-femoral and obdurator bypasses have been extremely useful in the successful management of these very difficult problems. Surprisingly, these relatively circuitous bypasses have proven to be fairly durable. The studies of Brief and others have illustrated that the five-year patency rates of femoral-femoral bypasses exceed 70 percent.[92] More than half of the axillary-femoral bypasses may be patent after two years, particularly if a femoral-femoral limb to the other side is added, thus increasing the volume of outflow. The ability to supply needed blood flow to the distal extremity before removal of the infected prosthetic implant has enabled the vascular surgeon to successfully manage problems which previously produced alarmingly high mortality rates.

Arterial Emboli

During the past two decades, arterial emboli have continued to present significant problems in diagnosis and management, but basic etiological factors appear to be changing.[93] For many years the most common causes of arterial emboli were congenital and acquired cardiac defects, and arrythmias. Prevention and correction of many cardiac defects have significantly reduced those

cases which eventually are complicated by arterial embolization. Cardiac arrhythmias continue to cause arterial emboli and are most often seen in association with arteriosclerotic heart disease. Myocardial infarcts with associated mural thrombi constitute another important source of emboli and it is therefore believed that most arterial emboli are of cardiac origin and are the direct result of arteriosclerotic heart disease. The insertion of prosthetic devices into the heart may lead to the generation of platelet aggregates and fibrin accumulations which may embolize. Emboli of platelets, fibrin and atheromatous debris may also emanate from ulcerative lesions in arteries afflicted with arteriosclerosis.[94] This is a common cause of cerebral vascular dysfunction.

One of the most important developments to appear during the rapid progress of vascular surgery in the past 15 years has been the introduction by Fogarty of balloon tipped catheters for extraction of clots.[95,96] These instruments have allowed removal of arterial emboli with a facility heretofore not possible. The importance of the techniques developed as a result of those studies leading to the Fogarty catheter cannot be overemphasized. Embolectomy under local anesthesia has become a common and successful method of extraction of intraarterial clots. Relief of arterial obstruction with minor operative procedures is in sharp contrast to the surgical techniques previously required to restore arterial continuity. The lower operative risk, successful extraction of clots, reduced operating time and wide applicability of this technique have resulted in less patient morbidity and in some cases a dramatic reduction in patient mortality. Of course, if the basic cause of the arterial embolization is not removed the patients are subject to recurrent episodes and may eventually die from the underlying cardiac disease that was responsible for the generation of the emboli. Nevertheless, these catheter techniques have had a pronounced influence not only in the management of thromboembolic disease but also in those procedures associated with *in situ* thrombosis. Reoperation with distal clot extraction has been made possible by these simple, more efficient techniques.

The aggressive application of the Fogarty catheter extraction of clots has inevitably resulted in some arterial damage and certain precautions must be observed if these procedures are to be successfully pursued.[96] Despite the relative fragility of the latex balloon, arterial rupture is possible and has been reported. In addition, repeated passage of the balloon produces intimal injury, and the tendency of the arterial wall to respond to injury by the deposition of arteriosclerotic plaques is well known. Intramural dissection, perforation, fragmentation of the balloons, kinking, difficult extraction and clot dissemination have been described. It is also obvious that antegrade removal of clots using balloon tipped catheters may because of the "snow plow" effect obstruct collateral channels. Despite these shortcomings, many of which can be overcome with proper techniques, these catheters are responsible for a spectacular and dramatic improvement in the management of arterial emboli, and mortality rates have been favorably influenced.

Thompson, Green, Perdue and their colleagues have described the changes in the management of arterial emboli.[93-95] Limb salvage in more than 90 percent of cases can now be achieved. Patient mortality has not decreased in all series because more seriously ill people are now considered candidates for surgical operation. Mortality rates of 10 to 15 percent are reported, but most deaths are in those patients with severe arteriosclerotic heart disease—many of whom would not have been previously considered to be candidates for surgical operation. Deaths as a direct result of surgical operation are less than 5 percent in most series.

Precise diagnosis, systemic heparinization, local anesthesia and early embolectomy are important features in this improvement. If these gains are to be consolidated, successful control of the underlying cause of the emboli must be achieved.

Cerebral Vascular Occlusive Disease

Arteriosclerotic occlusive disease of the extracranial cerebral vessels is an important cause of cerebral vascular insufficiency. Arterial dysplasia, trauma and extrinsic lesions may also produce sufficient disturbances in cerebral flow to induce cerebral ischemia. The relationship between extracranial vascular disease and stroke was obscured for many years because of the incomplete examination of the extracranial vessels. The standard pathological examination does not include direct visualization of the carotid and vertebral arteries in the neck. Patency is checked by the injection of saline and no morphological or histopathological studies are usually done. The relationship between completed strokes and preceding "small strokes" caused by recurrent episodes of cerebral ischemia was subsequently established. Many in-

vestigators, after examining these relationships, concluded that approximately half of the patients with nonhemorrhagic strokes had extracranial vascular disease.

The natural history of patients with cerebrovascular ischemia has often been misjudged. The retrospective study reported by Robinson, an evaluation of more than 1,000 patients with nonhemorrhagic stroke, showed that most patients did not get well following these episodes.[97] He reported that approximately one fifth of the patients died with the initial stroke, and of the survivors only a third eventually achieved complete recovery. The remaining people continued to have neurological disability and many also had recurrent symptoms. Acheson reported a prospective six-year study of 500 patients with cerebrovascular insufficiency.[98] Two thirds of these patients had more than one episode and only one third of the patients were free of symptoms at the end of the study period. Perhaps of more importance was the observation that of 151 patients with transient attacks of cerebral ischemia, in 60 percent a stroke eventually developed. These studies along with many others present strong evidence that the natural history of occlusive cerebrovascular disease is more dismal than suspected.[99,100] In fact, it appears clear that most people with strokes do not recover but symptoms continue and cerebral infarction is likely to develop.

Since the introduction of cerebral arteriography by Moniz in 1927 many thousands of studies have been done.[21] It is apparent that segmental arteriosclerosis and ulcerative plaques occur in the extracranial cerebral vessels as in other arteries. More than 50 percent of the patients have multiple lesions, of which some may be inaccessible. The most common patterns of involvement, however, include the presence of segmental lesions at the orifices and bifurcations of the carotid and vertebral arteries. Less frequently the intracranial portions of the basilar artery and internal carotid artery are affected. There may be, of course, associated stenotic or occlusive lesions of the great vessels at the arch.

Fields has shown that the circle of Willis as depicted in the anatomy books is intact in no more than 50 percent of patients.[101] Absence of a posterior communicating artery and variable patterns of the anterior cerebral arteries are often encountered and other congenital anomalies have been described. These collaterals have a bearing on the ability of the patient to cope with progressive stenosis and occlusion of extracranial arteries. The cerebrovascular cooperative study has elucidated the pattern of these arteriosclerotic lesions, and data derived from this study show the unfavorable influence inadequate collateral channels have on the natural history of this disease.

Careful biplane arteriograms of the intracranial and extracranial circulation, including the venous phase, have proven to be important in the proper management of cerebral vascular insufficiency. Clinical evaluation of the patients will usually provide significant clues as to the presence or absence of these lesions, but in approximately a third of the patients there may be no physical findings of extracranial vascular disease, despite it being shown by arteriograms.

The Doppler ultrasonic flow detector is useful in certain instances, especially if there is retrograde flow in the supraorbital arteries.[102] This suggests that there is occlusive disease and reduced pressure in the ipsilateral internal carotid artery. It is obvious that lesser degrees of stenosis or ulcerative plaques will not be detected by this method. Because the internal carotid is not accessible for palpation or direct examination, some form of visualization becomes imperative. Imaging techniques utilizing pulsed Doppler signals and computer analysis have shown the contours of the vessels, and may detect areas of significant arteriosclerosis. Small lesions and ulcerative plaques, however, remain beyond the definition of this technique. Similar problems are encountered with radionuclide imaging techniques, as previously described. The contours are too hazy and ill defined to allow the detection of small lesions.

Of the more innovative tests available, the new tomographic scanning technique promises to be of great value.[32] These procedures, controlled and analyzed by computer, utilize the basic principle of differing absorption of x-rays by various tissues. One may, therefore, develop cross-sectional images in which tissues with varying absorption coefficients may be separated. These studies are particularly useful in examination of the brain and especially in the detection of intracerebral hematomas and mass lesions. Further adaptation suggests that the instrument may be of assistance in assessing blood flow. It is apparent that these

newer scanning techniques will largely replace the classic brain scan. These studies are very useful in research, but their complexity and expense preclude their being used in all cases. These machines are therefore based in large diagnostic centers, and although they are of considerable value, angiography is still usually required.

On most vascular surgical services patients with cerebrovascular insufficiency are basically divided into four groups, according to types of symptoms. Some patients have transient attacks of cerebral ischemia, often called "TIA." These patients usually have transient neurologic dysfunction, often reflecting hemispheric involvement. In some cases there may be a total reduction in flow and perfusion which produces less precise symptoms. The mechanisms of production of these symptoms are thought to include the distal embolization of platelet, fibrin or atheromatous debris emanating from arteriosclerotic plaques at the bifurcation of the carotid. The emboli may also come from lesions in the aortic arch, great vessels and heart, but these are less frequent. DeBakey and his colleagues proposed the concept of "totality of cerebral blood flow," and stated that because of inefficient collateral circulation and associated segmental arteriosclerotic lesions, cerebral blood flow may fall below critical levels.[103] This perfusion defect may be aggravated by other arterial diseases, particularly heart failure and cardiac arrythmias. Hypovolemic or hypotensive episodes associated with serious illnesses or drug administration may further reduce cerebral flow. In some hypertensive patients vasospasm may occur, perhaps predisposing to the development of lacunar infarcts. All of these various disorders may, of course, cause transient attacks of cerebral ischemia and, if more severe, produce cerebral infarction.

Some patients admitted to hospital with cerebrovascular insufficiency have a progressive stroke, sometimes called a stroke in evolution. These patients have an unstable neurologic deficit and may progress to the third category, completed stroke. In some instances, however, the progressive stroke may resolve. Many patients with these changing neurologic signs have incomplete lesions, and may or may not be evolving a cerebral infarct. It is obvious that therapeutic intervention in some of these patients will evoke dramatic results, but the timing of operation is extremely important because the risk of extending a subclinical infarct is significant.

The third group of patients include those who have a completed or frank stroke and therefore are less frequently seen on a vascular surgical service. In these patients a cerebral infarct has occurred and can usually be clearly identified by examination. Diagnostic studies such as angiography may be hazardous and surgical intervention in many instances is fraught with danger. In most instances these patients are allowed to become neurologically stable before intervention is contemplated. Most vascular surgeons involved in the care of these patients believe that the severe neurologic deficit is the result of an established cerebral infarct and one is unlikely to be able to reverse the lesion. Moreover, the damage may be extended if all anemic infarct is converted to a hemorrhagic infarct. For this reason most physicians caring for these seriously ill patients recommend that the neurologic lesion be allowed to stabilize before intervention, usually requiring a period of two to four weeks.[100]

The fourth group of patients includes those who have an asymptomatic carotid bruit produced by a stenotic lesion. The indications for surgical operation in this group of patients are particularly difficult inasmuch as the natural history of all these lesions has not been adequately explored. Several provocative studies have been presented, however, the results of which strongly suggest that progression occurs in most of the patients and eventually symptoms supervene. Thompson and his associates have published data describing the natural history of more than 60 patients with carotid bruits produced by stenosis.[31] Over a five-year period strokes apparently related to this lesion developed in approximately 30 percent of these people. These data are consistent with those findings reported by Acheson.[98]

Serial angiographic studies presented by Javid are very pertinent.[104] In this careful prospective study approximately 100 patients were arteriographically examined annually to determine the natural history of carotid atheromata. Over a five-year period significant progression of the carotid atheromata was seen in 62 percent of patients, and in half of these the stenosis increased by more than 25 percent per year. Approximately a third of the patients had no change during this angiographic study. Of those patients in whom a significant increase in the stenosis was seen, signs

of cerebral vascular insufficiency developed in more than half. Progression of the lesions was more likely to occur in those patients who were hypertensive or symptomatic. Lesser degrees of stenosis progressed less rapidly. These data, combined with findings in studies presented from many vascular clinics, lend strong support to the concept that significant occlusive lesions of the extracranial carotid arteries are likely to progress to the point where they produce symptoms.[105] In most instances these will consist of transient attacks of cerebral ischemia, but some patients may have a frank stroke without the usual preceding "small strokes." For these reasons most vascular surgeons believe that preocclusive and highly stenotic lesions of the extracranial carotid artery should be repaired if the risk of operation is acceptably low.

Fields has proposed that patients in whom major vascular procedures are to be done where hypotension may be a complicating factor are very vulnerable to stroke if a tightly stenotic carotid artery is present.[104] The incidence of stroke in these patients is significantly higher and many doctors believe that in these people the carotid artery should be repaired before undertaking the major surgical procedure. An operative mortality rate of less than 0.5 percent has been reported in these patients.

Rapid changes have evolved in the operative and anesthetic techniques of carotid endarterectomy and most vascular surgery services have two distinct eras of management. Following the initial carotid operation by Eastcott, Pickering and Rob, and by DeBakey and his colleagues in 1953 carotid endarterectomy became one of the most frequently employed peripheral vascular procedures.[31] Many of the original operations were carried out under local or field-block anesthesia, permitting continuous evaluation of the neurological status of the patient. Some surgeons used the temporary inlying bypass shunt, a technique whose utility has been repeatedly proven by Thompson and his associates.[31]

Other surgeons prefer to employ general anesthesia and therefore careful attention is given to the type of anesthetic agent. It was shown that general anesthesia offered significant protection to the cerebral cortex from ischemia incurred during temporary occlusion of the carotid artery. A combination of barbituate and narcotic anesthesia combined with nitrous oxide also appears to provide some protection from cerebral ischemia. It has been shown on many occasions that patients who would not tolerate temporary occlusion of the carotid under local anesthesia do very well with general anesthesia. Halothane has been most often the anesthetic of choice.

During these studies, it became apparent that one of the most important features in the conduct of these operations was to maintain the blood pressure of the patient at or slightly above its normal level.[103] Induced hypertension, on the other hand, has proven not to be of much use and some investigators have suggested that it may actually be detrimental, producing competitive vasospasm. Similarly, it has been shown that the administration of vasoactive drugs is fraught with danger inasmuch as they may cause sudden hypotension which may produce sufficient ischemia to lead to a cerebral infarct.

The concept of utilizing hypercarbia as an adjunct to surgical procedures on the carotid artery was introduced by Wells, Keats and Cooley in 1962.[106] It has long been known that carbon dioxide and hydrogen ion concentration are important factors influencing cerebral blood flow. It was proposed by Cooley and his associates that the administration of hypercarbia during carotid occlusion would significantly increase cerebral blood flow and provide some protection from ischemia during the operation. Preliminary data supported this position, but findings in further studies by Ehrenfeld and his associates suggested that the converse might be true.[107] These workers, utilizing those principles initially described by Lassen, showed that in many patients maximum regional cerebral vasodilatation had already supervened as a result of the neurologic injury. The administration of additional carbon dioxide served only to dilate the other cerebral vessels, and when associated with fixed cerebral blood flow because of extracranial vascular lesions, the net result might be an "intracranial steal." If this situation obtained, they reasoned, hypercarbia would divert into more normal vessels a fixed volume of cerebral blood flow, and thus produce increased cerebral ischemia in the area of the recent neurologic insult. Because of these studies, and others, most anesthesiologists and vascular surgeons prefer that carbon dioxide not be manipulated, but kept within the normal range.

Although the data presented by Thompson, Gaspar and Javid strongly suggest that a tempo-

rary inlying bypass shunt is a safe and expedient method of maintaining cerebral blood flow during carotid reconstruction, other surgeons believe using the shunt may present an encumbrance to the operation.[100] It is suggested that those patients with small internal carotid arteries and highly placed carotid bifurcations are easier to manage without a shunt. It is apparent from data supplied by Wylie that in probably no more than 15 percent of patients is a shunt required during carotid endarterectomy.[100] The problem has been identification of the specific patients in whom this support is necessary. Techniques have been developed to assess this need and these include continuous electroencephalographic monitoring, a very sensitive method of determining significant reductions in blood flow.[108] Unfortunately interpretation of the electroencephalogram may be difficult, and this test does not expose ischemia occurring in the posterior circulation. Other methods of monitoring have included evaluation of ipsilateral jugular venous oxygen content. The initial reports by Lyons and his associates suggested this might be a helpful method of determining the need for additional support of cerebral circulation, but dissenting reports by Larson and Perry and associates indicated that anatomical lateralization was not consistent, and that many factors influenced the jugular venous content and saturation.[107,109] It is rarely employed today.

The most commonly used technique for evaluating the need for a shunt is to measure internal carotid back pressure in the intracranial circulation. This was initially proposed by Moore, Hall, Blaisdell and associates.[110] They suggested that an occluded "stump" pressure in the internal carotid artery of 25 mm of mercury or greater was an indication of adequate cerebral blood flow during carotid repair. If the patient had an established neurological deficit, a shunt was used regardless of pressure levels. Other data reported by Hays and co-workers suggest that the stump pressure should exceed 50 mm of mercury.[111] This is in agreement with findings in the experimental and clinical studies of Engell.[112] In patients with normal blood gas tensions and normal blood pH, an occluded distal carotid pressure of 50 mm of mercury correlates well with the blood flow requirements of the human brain, 54 ml per 100 grams of brain per minute. These studies support the concept of measurement of back pressure as a guide for the use of temporary carotid shunts.

The simple techniques initially described by DeWeese and Rob, Perry and co-workers have been useful in many vascular centers.[109,113] In this procedure the carotid artery is opened and the backflow from the internal carotid observed. If the retrograde arterial stream is brisk, bright red and pulsatile the operation is continued without the use of the shunt. In the event that the flow appears to be impeded a temporary inline shunt is inserted. It is obvious that a shunt will be employed in some cases where perhaps it is not needed, but in the view of Thompson and others this should present no problem. In fact, these very experienced investigators suggest that a shunt be used in all patients as a routine. Once facility is gained with its use it not only offers little encumbrance, but it acts as a stent to simplify the repair.

Simple endarterectomy of the carotid bifurcation is the usual procedure employed for arteriosclerosis, with careful attention to the separation of the distal plaque at the interface between normal and abnormal intima in both internal and external carotid arteries. Meticulous closure is usually satisfactory, although some surgeons prefer patch graft angioplasty. Resection and direct anastomosis or vein graft interposition is favored for treatment of dysplasia, but graduated dilatation of extensive multifocal lesions is useful in certain cases. All these procedures are very effective and quite durable.

Utilizing the techniques detailed in the preceding section, the mortality rate of carotid endarterectomy is reported in most vascular centers to be less than 1 percent. The rate of neurologic deficit incurred as a result of operation in most centers is reported as being less than 0.5 percent, although in 2 to 4 percent of the patients careful examination may show a transient deficit. It is apparent that in those patients who have a stroke in evolution higher morbidity and mortality rates may be encountered, particularly if the patients at the time of operation have a changing cerebral infarct. Most surgeons believe that operation on a patient with an acute severe stroke, particularly if associated with altered consciousness, is contraindicated. Mortality rates of up to 40 percent have been reported. It would appear that if a cerebral infarct is present, it is desirable to allow the patient to become neurologically stable before study or operation.[100] Operation for acute deficits may be useful in those patients in whom an in-

complete neurologic deficit has occurred, especially under direct observation. This may be seen in patients who are being prepared for surgical operation, after angiography or in rare cases, postoperatively. In other patients rapidly recurrent attacks of transient cerebral ischemia may be an indication for a relatively urgent operation and in some patients dramatic results have been obtained by this technique.[114] For the most part, however, emergency operations upon the stenotic carotid artery are rarely indicated.

The long-term results obtained by operation for cerebral vascular insufficiency have changed dramatically over the past decade.[31] With the current selection and management of the patients who have as presenting symptoms hemispheric signs of carotid insufficiency relief of these symptoms in more than 90 percent of cases can be expected. The late stroke rate in these patients is reported as being less than 5 percent when related to the operated artery. In those patients with more diffuse symptoms, rather than hemispheric, relief has been obtained in 60 to 80 percent of patients. The incidence of late stroke in these patients is also low, but it is well recognized that in patients who have predominantly vertebrobasilar symptoms, ultimate stroke is not as common as in those patients who present with symptoms related to the carotid territory. Nevertheless, significant improvement can be obtained in these patients if a neurologic deficit is not present at the time of operation.[100]

Of the nonsurgical methods currently used in the management of cerebral vascular insufficiency anticoagulation remains useful in some cases. Findings in studies of Baker, following a cooperative protocol, suggest that the main efficacy of anticoagulation is in those patients who have transient attacks of ischemia, apparently because of cerebral emboli.[115] Anticoagulation does not appear to be effective in the management of patients with neurologic deficits, or in progressive strokes. In fact, it is detrimental in these patients and produces a higher mortality than in the untreated group. Of more importance, however, is the current interest in the use of drugs which inhibit platelet aggregation. A cooperative study is in progress to evaluate the efficacy of aspirin in patients with cerebral vascular insufficiency. As alluded to in preceding sections there are numerous agents which are effective in reducing the tendency of platelets to aggregate and form arterial emboli, and these may be highly effective in these patients. Preliminary studies suggest this to be true but satisfactory controls have not been obtained and until the cooperative study is complete this issue is unsettled.

Visceral Arterial Disease

Arterial insufficiency as a result of stenotic or occlusive lesions in the celiac and mesenteric arteries has been described in many patients.[116] Arterial emboli have been reported to produce severe ischemia, particularly when in the superior mesenteric artery. Early identification of these syndromes is difficult and as a result morbidity and mortality rates are quite high. Recent advances in arteriographic techniques have enabled physicians to diagnose these problems at an early stage, before development of intestinal gangrene, and scattered reports of successful mesenteric artery embolectomy have appeared with increasing frequency.[116] Nevertheless, consistent diagnosis and early treatment is not often obtained. This is partly the result of associated illnesses because this syndrome is most likely to appear in people with severe cardiopulmonary disease, and in those who have low flow states produced by any cause. Nonocclusive intestinal ischemia may occur in such cases, particularly in those patients with congestive heart failure in whom digitalis is used, and in other patients when low flow occurs as a result of hypovolemia. If identified before the onset of intestinal gangrene, recovery is quite common, particularly if the underlying disease can be satisfactorily controlled. Unfortunately the serious nature of the associated disease often results in an unfavorable influence on the lifespan of the patient regardless of the outcome of the transient intestinal ischemia.

During the past decade there has been much interest focused on the concept of celiac and mesenteric artery insufficiency as a result of arteriosclerotic lesions, and in some instances extrinsic lesions producing partial stenosis of the celiac artery. Existence of a syndrome of median arcuate ligament compression of the celiac artery has been disputed for several years, and resolution of this problem is yet to be obtained.[117] Some investigators believe that because of anatomical differences the celiac artery may be located more cephalad, susceptible to compression by the median arcuate ligament of the diaphragm. It has been proposed that in these cases simple resec-

tion or incision of this ligament would release the celiac artery and allow restoration of normal blood flow. The operation has been used in many cases and in several series reported to be quite effective in relieving the vague symptoms associated with celiac artery insufficiency. Other investigators suggest that the syndrome does not occur except in association with occlusive disease in the superior and inferior mesenteric arterial systems. Szilagyi, and other investigators indicate that repair of the mesenteric artery circulation is effective and is all that is required. These workers state that they do not believe in the existence of an isolated median arcuate ligament compressing the celiac artery and producing symptoms.[118] On the other hand Stoney, Evans and others, following the initial reports by Marable, have described effective treatment of patients with visceral ischemia by operating upon entrapped celiac arteries with and without repair of mesenteric artery lesions.[119-121] It would appear, from the observations of these investigators, that ischemia in this area does occur and perhaps especially when more than one system is involved. Because of the lack of objective tests of intestinal ischemia, elucidation of this problem is incomplete. It is reasonable, however, to expect that in patients with abdominal angina, particularly those with multiple occlusive lesions, selective repair should be successful.

If visceral ischemia can be clinically identified angiograms are required for its final diagnosis and evaluation. In most cases, exclusive of those patients with emboli and the median arcuate ligament syndrome, the arteriosclerotic lesion is the typical segmental atheromata located at or just beyond the orifice. In the superior mesenteric artery this generally means in the first 2 cm of the artery, and the distal arterial bed is often, but not always spared. Once the lesion is identified and associated arteriosclerotic lesions evaluated operative repair usually consists of either thromboendarterectomy or bypass with autogenous tissue or a plastic graft. The most commonly employed solitary technique has been a bypass graft inserted end-to-side to the aorta and end-to-side to the superior mesenteric artery. Tube grafts of knitted Dacron have been most commonly employed and appear to be very effective in the management of this disease. In some cases associated arterial disease may require special techniques and more extensive reconstructive procedures.

The precise incidence of splanchnic artery aneurysms is unknown but they are apparently more common than usually appreciated, and the splenic artery is involved in more than half the cases.[122] In a review of 3,600 abdominal arteriograms where the splenic vessels were visualized, Stanley and co-workers reported 28 incidental splenic artery aneurysms, an incidence of 0.78 percent. These workers further showed that splenic aneurysms were more likely to occur in multiparous women or in young pregnant women, suggesting that the frequently observed medial degeneration was perhaps a result of hormonal influences during gestation. Arteriosclerotic splenic aneurysms do occur, but some workers have suggested that these may often be secondary to medial degeneration. An increased number of splenic artery aneurysms is seen in patients with portal hypertension and splenomegaly, and they may also occur in association with focal arterial inflammatory processes such as polyarteritis.

Assessment of the natural history of splenic artery aneurysms has prompted changes in management. The risk of rupture, except in symptomatic patients and young women during pregnancy, is less than previously thought. Stanley and his associates report a rupture rate of 5.3 percent except in these special categories.[123] Hypertension, of course, exerts an unfavorable influence, especially on large aneurysms. Because the mortality attending rupture of splenic artery aneurysms is approximately 25 percent, most vascular surgeons believe that early surgical treatment of these aneurysms is indicated if the operative mortality can be kept at an acceptably low rate, 1 percent or less. The indications for operation are more compelling in young pregnant women or in grand multiparous women. In other groups careful observation may be indicated, especially if calcification is present and the aneurysm can be followed with ease.[123]

Renovascular Disease

Lesions of the renal arteries as a cause of hypertension have received a tremendous amount of interest and research effort since the concepts were proposed by Goldblatt.[124] Although in most patients with hypertension, renovascular disease is not the cause, this is an important entity since it may yield to appropriate surgical therapy. It has been estimated that in 5 to 10 percent of patients with hypertension, renal arterial stenosis is the cause. This may constitute a significant problem, for as Foster and his associates at Vander-

bilt have reported in 1,000 hypertensive patients, renal artery lesions were found to be present in 460. Of the original series 39 percent, 176 of these patients, had renovascular hypertension.[125] This represented 16 percent of the entire group. This does not reflect the incidence of renovascular disease in the population as a whole because of the selectivity of the patient referral system. Nevertheless, it is a significant problem and deserves the special study it has received at several large centers.

Stewart and co-workers, Wylie, Foster, Fry and their associates have presented carefully detailed studies of the histopathological and morphological features of the lesions producing renovascular hypertension.[125-127] The pathological lesions can be divided into two groups, intimal and medial.[128,129] In the former group segmental stenosis is caused by atherosclerosis and intimal fibroplasia. Of those lesions involving the media of the artery, fibromuscular hyperplasia, medial fibroplasia and subadventitial fibroplasia are common. Associated extrinsic lesions may be found on occasion and intrarenal lesions may also be found, particularly with collagen diseases such as periarteritis. Trauma and renal infarcts and other retroperitoneal lesions may induce renal ischemia and subsequent renovascular hypertension, but are relatively uncommon.

From a functional point of view, rather than to divide the lesions according to pathologic findings it has been found more convenient to divide the lesions according to their morphologic characteristics.[129,130] Such a classification has importance both diagnostically and in regard to the natural history of the lesions. This classification divides them into three groups; focal, tubular and multifocal. Atherosclerosis, intimal fibroplasia and fibromuscular hyperplasia may produce focal lesions of the renal artery. The tubular lesions are usually caused by atherosclerosis and subadventitial fibroplasia. Atherosclerosis, medial fibroplasia and subadventitial fibroplasia may cause multifocal lesions, particularly common in the renal arteries. Medial fibroplasia produces the familiar "chain of lakes" or "string of beads" radiographic pictures so commonly associated with arterial dysplasia, and often erroneously called fibromuscular hyperplasia. There is no true hyperplasia in this variety, only dysplasia.

The natural history of these lesions is of extreme importance when deciding upon the indications for operative intervention.[130] As anticipated, the atherosclerotic lesions tend to progress, consistent with those changes occurring in other arteries. Unfortunately these lesions tend to occur in older patients and in those who have diffuse arterial disease. Therefore, the overall prognosis is somewhat less favorable than that encountered in patients with dysplastic lesions. Nevertheless, significant atherosclerotic lesions producing sufficient disturbances in renal blood flow to induce renovascular hypertension and posing a threat to the viability of the kidney may present compelling indications for operative intervention.

In those patients with renal dysplasia the focal lesions tend to proceed inexorably toward occlusion regardless of the underlying pathologic entity. In most cases these patients are younger and have renovascular hypertension. These lesions are particularly subject to local occlusion, intramural dissection, mural hemorrhage and in some patients malignant hypertension. Because of the tendency toward progression early operative treatment is indicated in most of these patients.[128-130]

In some patients with medial fibroplasia and multifocal lesions operative intervention will be indicated because of associated renovascular hypertension or threatened viability of the kidney. When encountered in its later stages, however, progression of this particular variety does not appear to be as rapid or as predictable as that of the focal lesions. If satisfactory blood pressure control can be obtained and renal viability is not threatened, nonoperative therapy may be successfully employed in these patients. Surgical intervention may occasionally be required at a later date, and repeated screening and angiographic procedures may be necessary in order to adequately follow the course of the disease. Assessment of the natural history of these lesions is of extreme importance in determining the requirements for operations. As has been pointed out by Foster and others, bilateral lesions tend to be metachronous and renal preservation is extremely important.[125] Nephrectomy as a primary mode of therapy is generally not indicated, since the surgeon may later be confronted by a severe lesion in the remaining kidney. Technical repair may not be possible at this later date. Every effort should be made to conserve renal tissue and early operation may reduce the risk of losing the kidney.

The diagnosis of renovascular hypertension remains difficult in some instances, but recent im-

provements in functional evaluation have been achieved. In most cases the diagnosis centers on the exposure of a significant arterial lesion and then subsequent proof of its functional activity. Those data reported from the University of California, San Francisco, in regard to arterial dysplastic lesions have suggested that more than 95 percent of patients can be cured of their renovascular hypertension when these lesions are identified at an early enough age and successfully repaired.[131] Functional tests, although obtained in these patients, have not been used in determining the need for operation. In most cases, and especially in those patients with atherosclerosis and multifocal lesions, assessment of the functional activity of the anatomic lesion is desirable before operation.[129,130]

The pioneering work of Howard and Stamey in evaluating bilateral renal function has been extremely useful, but these tests are not now used as often as in the past. Investigators at Vanderbilt still use split function tests in association with other studies and suggest that they have considerable value.[125] Newer tests of renal function, as reported by DeGrazia, utilize sophisticated isotopic techniques which allow simultaneous discrimination of renal excretory function and renal plasma flow.[132] These studies, while somewhat expensive, promise to be of great value in studying renovascular hypertension, and have the advantage of not requiring cannulation of vessels, or ureteral intubation. Numerous procedures have been proposed for the evaluation of renovascular hypertension, but most vascular centers caring for these patients have a protocol which employs the more reliable and simpler tests. It is apparent that more than the intravenous pyelogram (IVP) is necessary because it will indicate only about a third of those patients in whom renovascular hypertension is later shown to exist. The most commonly employed diagnostic protocol is similar to that devised at the hypertension center at Vanderbilt, and includes a 24-hour urine specimen for measurement of creatinine clearance, electrolytes, cathecholamines, vanillyl mandelic acid, 17 hydroxy steroids and ketosteroids. Subsequently a rapid sequence urogram is obtained and then renal arteriography and renin assay.[125]

The determination of plasma renin activity is important both in diagnosis and in establishing the prognosis in these patients. There are various techniques used in these studies, but the object of the test is to detect an increase in renin production from the affected kidney. This may be augmented by salt depletion, administration of hydralazine, bringing the patient into the erect position or by other provocative maneuvers. The basic aim is to show when there is an increased renin production by the affected kidney and then confer upon the anatomical lesion functional activity. In those patients who have unilateral disease a renal vein renin ratio between abnormal and normal of 1.4 or greater is often sought, but it has been recognized that autonomy may develop in some patients.[133] Peripheral renin activity may be normal and renal vein renin levels may be normal, even though an arterial lesion correctable by surgical operation is present. This is particularly likely to be the case when functioning arterial collaterals can be shown. Such arteriographic features are of considerable diagnostic importance. False negative findings, therefore, do occur in a small number of cases, and although the determination of plasma renin activity is the test for renovascular hypertension, it is not infallible.

The physiologic basis for the determination of plasma renin activity centers around the production of renin by the juxtagomerular apparatus adjacent to the afferent artery.[134] This substance is secreted into the kidney and into the lymph, and subsequently acts upon an alpha-2-globulin to produce angiotensin I, a decapeptide. Plasma and pulmonary converting enzymes act upon this decapeptide and produce the octapeptide angiotensin II. This is the active pressor agent which ultimately acts to increase arterial resistance. In addition, it stimulates the production of aldosterone and in a short loop negative feedback mechanism decreases its own production. It is subsequently hydrolyzed by peptidases into peptides and amino acids and thus rapidly destroyed.

Renin release is largely under the control of three different mechanisms. There are intrarenal receptors which are directly responsible for the production of renin and the renal nerves exert a modulating influence on this activity. In addition, certain humoral agents affect the production of renin and generally act in concert with those other processes. Most investigators agree that the vascular receptor within the wall of the afferent arteriole is dominant in this relationship and responds to changes in transmural pressure. This effect is modulated by the renal sympathetic nerve activity and by intrinsic myogenic factors, and

also may be subject to changes produced by alterations in elastic components of the wall. Nevertheless it appears that changes in wall tension are largely responsible for renin release.[131]

The macula densa apparently harbors a sodium sensitive mechanism which, according to some investigators, effects a nephron by nephron control of blood flow by responding to changes in sodium concentration in the distal renal tubule. This mechanism can be shown to be independent of the activity of the vascular receptor, but appears to have a less prominent role in renin control. Catecholamines, steroids, sodium and potassium ions all may influence renin production. Angiotensin II and antidiuretic hormone (ADH) are also involved in a short loop negative feedback system.

Initially the management of renovascular hypertension in patients with unilateral lesions was nephrectomy, and this was often an effective mode of therapy. Because of metachronous lesions, however, it is no longer acceptable to resect the kidney except in those instances in which repair may not be possible. Freeman and Wylie pioneered in renal artery reconstruction by endarterectomy, but the bypass techniques have proven to be more popular among most vascular surgeons.[130] Transaortic renal endarterectomy and appropriate repair with or without angioplastic techniques have been very useful. Autogenous and plastic prosthetic aortorenal bypasses are currently the most commonly used procedures. As mentioned in previous sections, the late behavior of these antogenous bypasses introduces some cause of concern, especially because uniform dilatation has supervened in a few patients. Only a very small proportion, 2 to 4 percent, have become aneurysmal, and these appear stable.[48,49] Serial angiographic procedures are currently in progress to investigate the long-term behavior of these arterial conduits, and there is considerable discussion as to which type of autogenous tissue is most useful, saphenous vein or hypogastric artery. The issue at present is unsettled as both appear to be very useful in the management of these diseases, complications occurring in only a very few cases.[125,128,131] In some patients aortorenal bypasses done using Dacron prosthetic implants have also been effective, and many large centers report excellent long-term behavior of these grafts.

It is apparent that those patients who have fibromuscular dysplasia can be expected to respond satisfactorily to this operation, and success rates exceeding 95 percent have been reported from many institutions. In contrast are those patients with multifocal lesions in whom the results of operation are less dramatic.[129] Nevertheless, substantial gains can be expected, and up to two thirds of the patients can be benefited by appropriate repair techniques. In some, the administration of small amounts of antihypertensive drugs may be required in order to maintain satisfactory blood pressure levels. In addition, preservation of renal tissue is possible in many of these cases and there are persuasive data indicating that in many cases it has been possible to avoid nephrectomy because of new developments in reconstructive techniques.

Autotransplantation with temporary perfusion of the kidney, techniques developed during renal transplantation, have enabled vascular surgeons to repair lesions in small renal artery branches which previously would not yield to other techniques. Operations have been reported by Lim, Foster and others and it is apparent that before removing even what initially appears to be an inoperable kidney, these exogenous repair techniques should be undertaken.[135,136] In many cases they will enable vascular surgeons to preserve a kidney which would otherwise be doomed to nephrectomy.

Special techniques have been successful in treating renal arterial dysplasia. Graduated dilatation is useful here, as in other arteries, and especially in small branches.[137] If resection and replacement are not feasible, such intraluminal remodeling may be very helpful. Microsurgical procedures are of particular use in these cases, and their application is facilitated by autotransplantation techniques.

Several large centers have now reported on results 10 years after renal artery reconstruction. The initially successful effect has been sustained in most instances, and if contralateral disease has not supervened, the results of these operations have proven to be remarkably durable. This is especially likely in those patients with medial dysplasia. The reports of the cooperative study on renovascular hypertension showed that of 502 patients with renal artery stenosis and coexisting hypertension, following repair 51 percent were cured, 15 percent were improved and 34 percent failed to respond.[138,139] The operative mortality was 5.9 percent. With unilateral fibromuscular

disease a favorable blood pressure response was seen in 79.8 percent while in those with unilateral arteriosclerosis 63 percent were benefited. In those patients with bilateral stenosis a favorable result occurred in only 56 percent. From the data recovered from this study certain conclusions are presented, suggesting corrective surgical procedures are especially useful in unilateral disease when there is evidence of functional renal disparity judged by various diagnostic tests. In patients who have bilateral renal artery stenosis, repair is frequently effective and the side with the greatest functional disturbance should be initially reconstructed. Subsequently, the decision to repair the other side would be determined by the patient's response and the results of the various tests. The directors of the cooperative study concluded by indicating that in their opinion an operative procedure should be considered in patients who have moderate to severe hypertension that is refractive to drug therapy, and in people in whom preservation of renal tissue is an important consideration.[139]

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Perils of Oxygen Toxicity in Treating the Adult Respiratory Distress Syndrome

One tries to deliver oxygen to patients with adult respiratory distress syndrome but one cannot give oxygen with impunity . . . I think it's now safe to say that the administration of high concentrations of oxygen for more than three or four days will lead to lung damage. In fact, in one study carried out in our hospital, one could get physiological evidence of impairment of pulmonary function after 36 hours of administration of 100 percent oxygen.

One should bear the familiar oxyhemoglobin dissociation curve in mind, and one key number to remember, because it's very useful clinically, is an arterial oxygen pressure (Po_2) of 60. A value of 60 is at the shoulder of the curve and is approximately 90 percent saturation. So that if your Po_2 is over 60, you're in pretty good shape in terms of providing about as much oxygen to that amount of blood as it can contain. And there's no sense having a Po_2 of 300 because that adds very little more oxygen to the bloodstream and has a much greater injurious effect on the lung. So try to keep Po_2's in the neighborhood of 60—and in some of these patients 60 is a luxury and more than you can get and sometimes you have to settle for 50 or even 40. Another important number to remember is 40, which is 75 percent saturated. If you're using mixed venous oxygen tension as a guide to adequate delivery of oxygen, the number we use clinically is about 30 mm of mercury. We'd like to have it higher than that. Again, sometimes it's difficult to achieve this value.

—DICK D. BRIGGS, JR., MD, *Birmingham, Alabama*
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Refer to: Choriocarcinoma and gestational trophoblastic disease—Medical Staff Conference, University of California, San Francisco. West J Med 124:219-225, Mar 1976

Medical Staff Conference

Choriocarcinoma and Gestational Trophoblastic Disease

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *The topic of Medical Grand Rounds this morning is choriocarcinoma and gestational trophoblastic disease. We have asked Dr. Michael Friedman of our Cancer Research Institute to discuss this relatively uncommon disorder.*

DR. FRIEDMAN:† For centuries physicians have studied gestational trophoblastic diseases with increasing interest. Perhaps the first written description of a molar pregnancy was offered by Hippocrates (Aphorisms 1.45): "When women, in a moderate condition of body, miscarry in the second or third month, without any obvious cause, their cotyledones are filled with mucosity, and cannot support the weight of the fetus, but are broken asunder." Today, tumors of this family of diseases are of interest not merely because they are neoplasms responsive to chemotherapy, but also because they represent an almost ideal model system for the general study of malignant disease. Focusing on gestational trophoblastic disease, we confront questions of cellular growth and differentiation that are central to human biology and embryology. Furthermore, we must deal with important immunologic issues relating to fetal and tumor antigen recognition—currently an attractive subject because of the renaissance of interest in immunotherapy. And finally, we have access to cellular kinetic information that directs rational therapy (in contrast to the usual empiric approaches).

Trophoblastic disease includes three related conditions: (1) molar pregnancy, (2) metastatic molar disease (chorioadenoma destruens) and (3) choriocarcinoma. These entities may occur as isolated diseases or one may follow another in a particular patient. Most commonly these diseases are associated with pregnancy, but their occurrence may be nongestational as well. Often choriocarcinoma occurs as a perigestational event, but it may arise as a primary tumor of the mediastinum or retroperitoneum that is unassociated with pregnancy, and when it does the prognosis will be less hopeful. The histopathologic distinctions between these tumors are crucial. Differentiation between locally invasive mole, metastatic mole and true metastatic choriocarcinoma directs the treatment regimen and predicts the response

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ABBREVIATIONS USED IN TEXT

DNA = deoxyribonucleic acid
HCG = human chorionic gonadotropin
LH = luteinizing hormone
TBG = thyroxine-binding globulin
TSH = thyroid-stimulating hormone

to therapy and the curability. It is necessary to classify each patient's disease in terms of gestational association, histopathologic criteria and extent of metastasis.

The placenta (the initial common tissue for these tumors) is composed of normal trophoblastic elements. Viewed microscopically it evidences cellular pleomorphism, vascular invasion and nuclear atypia. Recognizing the usual biologic activity of a placenta (aggressive local encroachment and early vascular invasion), one wonders why it is not commonly considered a malignant tissue. More provocative perhaps is the fact that during pregnancy, and especially at the time of delivery, a large volume of placental tissue is deported from the pelvis to the pulmonary vasculature. This phenomenon, except when it is noticed during the occasional attendant cardiovascular or hemostatic problem, is clinically unrecognized. Rarely is placental tissue radiologically evident in the maternal lungs after a delivery. What is it about placental tissue that makes it unique among normal tissues and confers on it some malignant characteristics? Perhaps investigating the normal trophoblast provides some insight into why malignant trophoblastic disease has the potential for growth and spread and why it responds to treatment the way it does. Trophoblastic growth may be thought of as points on a continuum ranging from a benign state (normal placental tissue) through more malignant states (molar pregnancy and metastatic mole or chorioadenoma destruens), to the most malignant situation, choriocarcinoma. All of these display similar cellular elements (elements in common with normal trophoblastic tissue), and they all share the same repertoire of elaborated hormones.

Hydatid mole is easily recognized grossly, and pathophysiologically it represents massive hydropic degeneration of the villi (an overt failure of the maternal and fetal vessels to join properly, and with villi that are still microscopically clearly visible). That this condition is relatively uncommon in the United States should in no way influence our perspective of the worldwide impact of this disease. In Formosa, parts of Southeast Asia and Central America it is a common problem, and is present in almost 1 percent of the pregnancies observed. In the United States only between one in 1,000 and one in 3,000 pregnancies are molar in nature.[1] Moles can be seen as either locally invasive or distantly metastatic. Since a local or metastatic mole is easier to treat and cure than a choriocarcinoma, the distinction between them is a crucial one. Choriocarcinoma, whether it is locally present or widely metastatic, is the most malignant member of this family, and it is the most difficult to treat. Microscopically, choriocarcinoma lacks villous structure, differentiating it from molar disease. This tumor can be widely aggressive and involve most of the organs of the body. The single most common location for metastatic spread is the lung (70 percent in most series). Local genital tract involvement is fairly common (20 to 30 percent), and probably results from direct spread at the time of evacuation or curettage.[2] Virtually any organ system can be affected, but perhaps the most significant site is the central nervous system, where metastases are of dire consequence. In considering the diagnosis of choriocarcinoma in a patient, one must histologically confirm a metastatic nodule in order to initiate a proper therapy.

The association of choriocarcinoma with molar pregnancy is well recognized but the two are not always connected; and at the time of diagnosis of a mole it is impossible to predict what malignant sequelae, if any, will follow. Even in normal pregnancy subsequent choriocarcinoma is sometimes seen. Focal dysplastic or neoplastic sites are probably present in normal placenta; but the technical difficulties one encounters in scanning several square meters of normal placental tissue to look for such tiny areas makes this procedure unrewarding. Possibly many of the placentae that are considered normal have microscopic abnormalities that are not detected by gross techniques. Consequently, the incidence of abnormalities is underestimated. Malignant trophoblastic sequelae are noted in 10 to 20 percent of women who have molar pregnancy. About two thirds of this group (or approximately 10 percent of those with molar pregnancies) will have either locally invasive or metastatic molar tissue. About one third (approximately 5 percent of the entire group) will have frank choriocarcinoma. Alternatively though, almost half of patients who have choriocarcinoma have not had an associated, documented preg-

nancy. Some choriocarcinomas arise in nongestational areas (mediastinum or retroperitoneum); but perhaps there are abortions that are spontaneous, missed or not reported to physicians in which unrecognized choriocarcinomatous elements are present.

In a patient who has had a molar pregnancy and subsequently presents with pulmonary nodules, a lung biopsy should be done to determine whether this tissue is composed of villous elements and therefore is metastatic mole, or whether it has none of these elements and represents choriocarcinoma, a much more serious disease.

These trophoblastic tumors are intriguing because of their biochemical and endocrinologic uniqueness. The large repertoire of products elaborated by normal and malignant trophoblastic tissues include steroids (progesterone and estrogenic compounds), protein hormones (human chorionic gonadotropin, thyrotropin and placental lactogenic hormone) and probably a variety of other products which have not as yet been completely identified. Human chorionic gonadotropin (HCG) is the tumor product of biologic and clinical significance. HCG is a glycoprotein of two subunits, an alpha and beta chain. The alpha chain is structurally similar to that of luteinizing hormone (LH) and to thyroid-stimulating hormone (TSH). This similarity is probably responsible for the striking high thyroxine (T_4) levels seen in some patients with mole and choriocarcinoma (an issue separate from that of the physiologic increase in thyroxine-binding globulin [TBG]). Interestingly though, these high T_4 levels are rarely, if ever, associated with clinically prominent hyperthyroidism. The second chain of this glycoprotein, the beta subunit, provides the antigenic uniqueness to HCG. The beta subunit permits a radioimmunoassay which specifically and sensitively detects HCG (with little overlap with luteinizing hormone). The pregnancy test, as it is commonly carried out, indicates grossly elevated HCG levels, but probably 30 percent of women with choriocarcinoma and elevated levels of HCG are not identified by the common pregnancy test. There are a variety of other tests to sensitively detect HCG titers, the most specific of which is evaluation of the beta subunit HCG by radioimmunoassay.

After termination of a normal pregnancy a predictable decrease in HCG titer levels occurs, and by the eighth postpartum week these values are in the normal range of physiologic luteinizing hormone secretion. However, about one fifth of patients with molar pregnancy continue to have an elevated HCG titer at eight weeks after their curettage or abortion, and in approximately one half to three quarters of that subgroup further malignant sequelae develop. Clearly then, it is necessary to obtain follow-up serial HCG titer studies (preferably of specific beta subunit HCG titers) on all women with molar pregnancies. By means of these titer studies, patients at high risk can be identified and chemotherapy can be instituted at the earliest possible moment. In a study of 92 patients with active trophoblastic disease, Bagshawe noted that in only 4 patients were there urinary excretions less than 1,000 international units (IU) of HCG in 24 hours and in 16 patients they were greater than 1,000,000 IU. In most of the patients there were titers falling between these values.[1] It has been estimated that the presence of as few as 1,000 trophoblastic cells can be detected by specific beta subunit assays, and this clinical sensitivity is unparalleled in oncology. No other tumor gives us evidence of the presence of such a tiny amount of disease. The amount of myeloma protein certainly helps in judging disease activity in multiple myeloma, but it never pro-

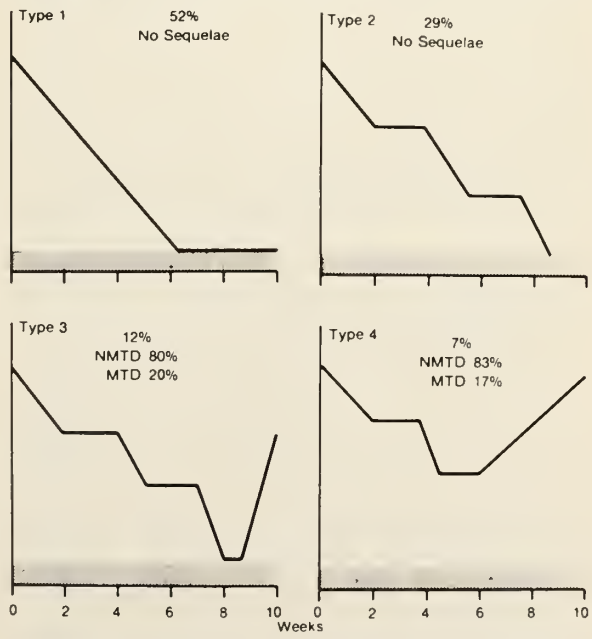

Figure 1.—Four types of gonadotropin regression slopes observed following evacuation in 116 untreated patients with molar pregnancy. Complications were limited to patients with type 3 and type 4 patterns. Percentages indicate relative frequency of nonmetastatic trophoblastic disease (NMTD) and metastatic trophoblastic disease (MTD) in each group. (Reproduced with permission from **JAMA** 220:209-213, Apr 10, 1972; Copyright 1972, American Medical Association.[1])

vides this accuracy in determining minimal tumor cellular burden. Knowing the kinetics of the HCG curve of patients who have had molar pregnancies can be of great predictive value as well. Goldstein[4] has shown (Figure 1) that in most of his patients there either was a rapid direct fall in HCG back to normal levels or a slower, steady, stair-step regression back to the normal range, with no evidence of further malignant sequelae. In contrast, in a minority of patients there were either transient near-normal levels which then rose rapidly or else persistently elevated values. In a patient in whom HCG levels are elevated, immediate intensive diagnostic study followed by therapy should be undertaken. Patients who have had molar pregnancy should be observed for several months to ensure that the normalization of this value is not a brief one but is actually a permanent one.

In evaluating patients with known or suspected metastatic choriocarcinoma, one must first define the sites of involvement of disease. Lungs and genital tract are common sites for the disease; metastases to these areas are highly responsive to therapy. Central nervous system involvement, however, has a more dire prognostic significance since intracranial bleeding is common. Patients with central nervous system involvement require both irradiation to the entire cranium and intrathecal methotrexate. The clinical status of the central nervous system can be determined by means of EMI®* scanning, radionuclide brain scan and, occasionally, arteriographic studies. Determining HCG levels in samples of cerebrospinal fluid and comparing them to those found in serum is also useful. Second, height of the HCG titer is important in evaluation of these patients. The duration of disease, judged from the time of abortion or evacuation to the time metastatic disease is detected, as well as the titer of HCG are useful prognostic guides. Women with early disease of short duration and with low titers responded well to therapy, and 95 percent appeared to be completely cured. But if the disease has progressed for over four months and the HCG titers are in excess of 1,000,000, the cure rate is much lower. The risk of death is higher with advanced disease of long duration and with a high titer. Treatment of a high-risk patient with a single drug is inadequate; multiple chemotherapeutic agents should be employed.

*Manufactured by EMI Medical, Inc., 3605 Woodhead Drive, Northbrook, IL 60062.

The chemotherapy of choriocarcinoma is a bright spot in adult malignant disease and a subject dear to the hearts of chemotherapists. There are few diseases the responses of which are so dramatically complete and predictable.

Since 1957, when methotrexate was first shown to be curative for choriocarcinoma (by Hertz and Li at the National Cancer Institute), an increasing body of information has accumulated suggesting that methotrexate is not only the standard drug, but may in fact be the primary drug for the treatment of choriocarcinoma. The unique efficacy of methotrexate in this disease may relate to the peculiar folate requirements of the pregnant mother, the fetus and the placenta. Women whose diets usually supply adequate folate become folate deficient in pregnancy. Not enough is known about the folic acid metabolism of placental tissue, but perhaps one reason methotrexate is such an effective drug is that it is a potent antifol. It has been estimated that nearly 90 percent of patients with early choriocarcinoma can be cured with methotrexate and that 40 percent of patients with more advanced disease are cured with only this single agent.[1]

In addition, a variety of other agents are effective in treating choriocarcinoma. Dactinomycin (Cosmegen®) is probably as effective as metho-

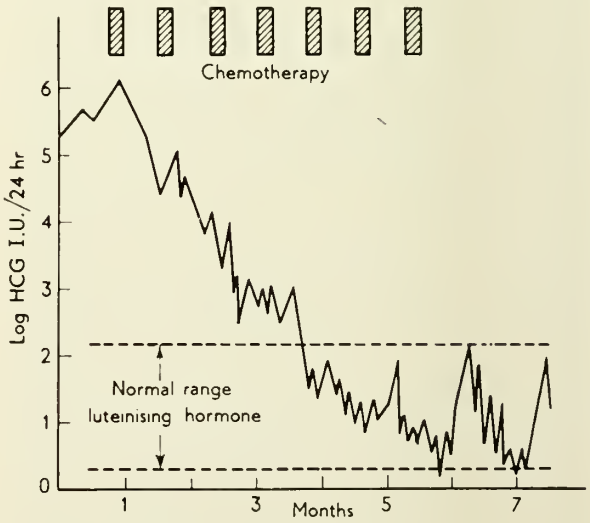

Figure 2.—The fall in human chorionic gonadotropin (HCG) excretion during treatment by chemotherapy is a more or less irregular curve as shown here. Below about 250 IU per day the contribution of luteinizing hormone to the measured gonadotropin output becomes substantial and variation in the range equivalent to 10 to 150 IU. Excretion of HCG per day may be wholly attributable to fluctuations in luteinizing hormone production. (Reproduced with permission from author and publisher, Ref. 1.)

trexate in curing early and advanced disease;[5] 6-mercaptopurine (Purinethol®) and the vinca-alkaloids, vincristine (Oncovin®) and vinblastine (Velban®) have been shown to be useful in curing early disease and in ameliorating advanced disease.[1] Combinations of these drugs have been employed in treating prognostically poor situations; 6-mercaptopurine plus methotrexate have been shown to be effective; actinomycin D together with vincristine and methotrexate in combination have been used effectively, as have combinations of actinomycin D, chlorambucil (Leukeran®), and methotrexate. In some respects, all of these therapies are similar to regimens used effectively to treat patients with testicular cancer.

Figure 2 depicts the response of one of Bagshawe's patients in whom chemotherapy pulses were given.[2] Chemotherapy was effective in destroying tumor cells. Although an initial rise in HCG associated with cellular dissolution occurred, HCG fell steadily and fairly rapidly to within normal range. One might ask why chemotherapy should be continued for several cycles past the point at which normal HCG values are noted. Within this normal range a few viable cells could occultly persist; thus, to ensure complete eradication of all tumor, therapy must be continued beyond the time of normal HCG values. A kinetic model that nicely fits this situation can be described: Clinically detectable tumor burden is 10^9 or 10^{10} cells; our ability to assess amounts of tumor less than this would not be possible if it were not for this biochemical marker. With effective therapy, a persistent fall in tumor number occurs throughout the entire period of treatment. Choriocarcinoma is a tumor with a high growth fraction (proportion of cells actively dividing), and it infrequently exhibits clinical resistance to methotrexate. It is possible, by computing and extrapolating the slope of this curve, to predict the time when the last cell should be killed (the intercept between time and 0 cells). In this way we can estimate how long the patient should be treated (Figure 3). While these theoretic considerations are portrayed as clean and obvious, the clinical situation may be more complicated and refractory. Figure 4 shows four relapses of disease. The patient was treated with a combination chemotherapy on three occasions and, on the last, hysterectomy and therapy with combination of methotrexate, 6-mercaptopurine and actinomycin D were carried out. On each occasion the patient improved. The apex of the HCG curve is progressively lower in each instance, suggesting that although the tumor volume had increased, the curve had not reached its previous height.

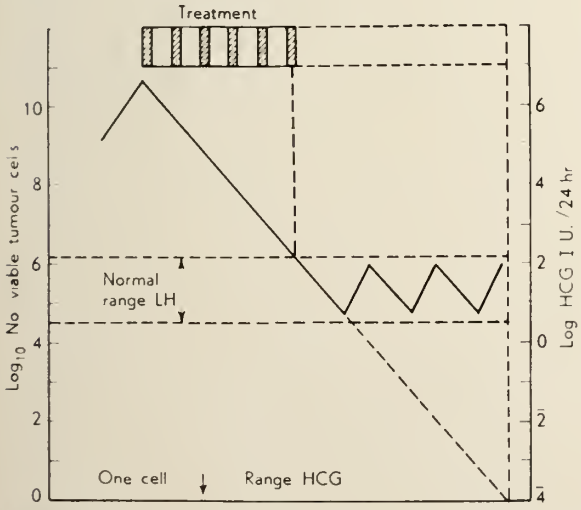

Figure 3.—By plotting a regression line through the values for human chorionic gonadotropin (HCG) excretion during treatment, the relationship between HCG excretion, normal luteinizing hormone (LH) production and the amount of hormone produced by "one cell" can be illustrated. The relationship emphasizes the need to continue treatment after normal gonadotropin values have been reached. (Reproduced with permission from author and publisher, Ref. 1.)

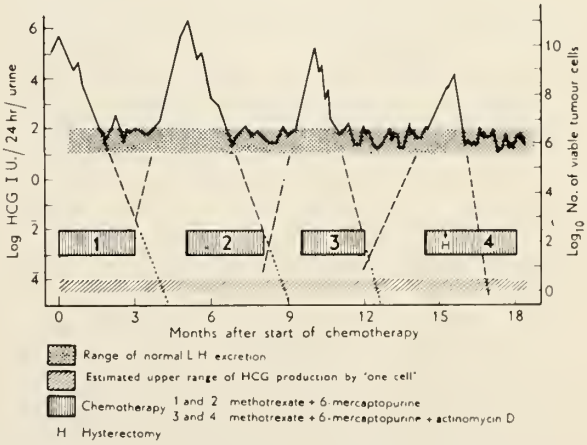

Figure 4.—Human chorionic gonadotropin (HCG) in a patient who relapsed three times after the initial response to chemotherapy. Extrapolation of the hormone descent and ascent curves from the time of completion of each series of courses of treatment is related to the estimated number of tumor cells. The first three courses of treatment were discontinued before the descent slopes intersected the "one cell" range. It should be noted that this type of analysis can be applied to only a small number of cases because the descending HCG curve is often too irregular for a useful regression line to be drawn. LH refers to leuteinizing hormone. (Reproduced with permission from author and publisher, Ref. 1.)

This case also suggests that therapy was discontinued too soon and that relapses could have been prevented by continuing therapy. The patient was eventually cured by surgical intervention and a fourth intensive course of chemotherapy. For patients with such resistant disease (for such refractory and poor-risk patients) a combination therapy is essential and offers curative potential.

The immunological aspects of this tumor are fascinating, and as a biological experiment pregnancy is an almost unparalleled phenomenon. Why is it that the fetus, a very potent antigen, is so well tolerated for the full term of pregnancy? The mother's immune response is not completely suppressed (although immunologically she is a somewhat compromised hostess), the fetal antigens are potent inducers of antibody response and the placenta is not an immunologic sanctuary. We really do not know why this foreign material is tolerated so well. It has been theorized that the infrequency of metastatic trophoblastic disease and the ease with which we cure it is somehow related to the fact that powerful immunological factors, currently incompletely identified, are at work. Several attempts to study this problem have been made. Studies of the histocompatability of placental antigens and studies in which fetal-maternal histocompatability profiles have been compared have yielded contradictory results. One group of investigators stated that in cases in which histocompatability exists, the risk of uncontrolled malignant metastatic disease is higher; but Terasaki and others have failed to make this kind of correlation. Clearly, however, some patients who have glaringly incompatible HL-A fetal-maternal profiles die of metastatic disease, and others who have compatible HL-A fetal-maternal profiles are entirely cured of disease. By itself, HL-A typing is an insufficient determinant of response.[1]

The therapeutic implications of these immunologic differences between patient and tumor have been exploited, and some ingenious immunological experiments have been carried out. Specific active immunization by means of a variety of agents has been attempted to promote immunologic rejection of the tumor. Anti-husband sperm antibodies have been injected intravenously into the affected woman, the husband's skin has been grafted onto the affected woman and leukocytes from the husband have been injected intravenously. Some nonspecific approaches, such as bacillus Calmette-Guerin (BCG) immunization and transfer factor injections have been attempted as well. Some patients may have benefited from these trials; but to date, evidence of benefit is equivocal and these procedures must be regarded as purely investigational.

A related immunologic issue, the role of HCG in the enhanced malignant potential of choriocarcinoma, requires further investigation. A growing body of evidence suggests that HCG is a potent immunosuppressive agent itself. Laboratory animals given high doses of HCG are less able to reject tumor burden and are more susceptible to particular bacterial infections. The finding that women who receive HCG (for example, for attempted weight control) show depressed humoral and cellular immunity is even more relevant and may offer a partial explanation for the association between high titers of HCG and poor prognosis. A vicious spiral can be envisioned with the development of high HCG levels, increasing tumor burden, less ability to reject the tumor and progressive disease. Other products of the trophoblast (progesterone, for example) may act similarly.

One of the thorniest issues in the treatment of malignant trophoblastic disease is the place of prophylactic therapy for patients with molar pregnancies. Early disease is easily treated and curable; the longer the duration of disease and the greater the amount of involvement, the less the chance of complete cure. If there is a therapy which is effective and reasonably safe, should all patients who have molar pregnancy receive adjunctive chemotherapy as a prophylactic measure at the time of preliminary evaluation? There is no single answer to this question; a physician must elect either to observe the patient carefully or to initiate chemotherapy immediately. No matter which course is chosen, all patients should be meticulously examined weekly. Serial HCG titers should be accurately and reproducibly carried out and any changes on x-ray films of the chest noted. If a patient can be watched in this way, if she is reliably compliant and if the physician has at his disposal proper laboratory support, then vigilance is an appropriate course to follow.

When a physician elects to withhold chemotherapy from a patient after termination of molar pregnancy, he or she must follow this type of protocol. Specific beta subunit determination should be done when the HCG levels are near physiologic range and overlap with LH. The indications for chemotherapy are unequivocal. Persistent HCG titers after 6 to 8 weeks, or plateauing or rising HCG titer indicate persistent or meta-

static disease. For complete restaging x-ray study of the chest and brain scan should be carried out, and single- or multiple-agent therapy should be administered promptly.

The alternative of immediate chemotherapy may be elected. Some investigators, however, have raised objections to the routine prophylactic treatment of molar pregnancy. First, most patients who are primarily treated surgically, or who have an abortion, are cured; and it is only in 20 to 25 percent of patients that malignant sequelae later develop. Therefore, routine adjuvant therapy would treat patients who might not need it. Second, although it must be noted that 10 to 20 percent of patients die of progressive disease, most patients in whom malignant sequelae develop in the postevacuation period can be cured. Third, minimal drug toxicity is the rule but exceptional toxicity is occasionally noted. However, methotrexate administered twice weekly is effective and causes minimal toxicity. Fourth, young women of reproductive age exposed to mutagens may suffer consequences of tetratogenic damage or may incur an enhanced risk of neoplastic disease themselves. The same risks are probably present with the use of actinomycin D and radiotherapy, which are known to intercalate with or change deoxyribonucleic acid (DNA). However, much evidence exists to suggest that methotrexate is a safer and less mutagenic agent than some other drugs might be in this type of situation.

An adjuvant regimen of proved efficacy is the use of methotrexate, 0.6 mg per kg of body weight given intramuscularly twice weekly for three weeks (six doses). In a comparative trial by Holland, women with evacuated molar pregnancies received either placebo or twice-weekly methotrexate. In eight of 65 patients randomly assigned to treatment with placebo, there were malignant sequelae. In none of the 55 patients treated with methotrexate twice weekly was there evidence of malignant progression, and in these patients there was no significant hepatic or hematologic toxicity. As expected, most of the placebo-treated patients in whom progressive malignancy occurred were subsequently successfully treated.[6]

Long ago, Hippocrates captured the essence of the dilemma posed by the treatment of this disease: ". . . the occasion fleeting, experience fallacious, and judgment difficult. The physician must not only be prepared to do what is right himself, but also make the patient, the attendants, and externals cooperate." (Aphorisms 1.1)

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Important Advances in Clinical Medicine

Epitomes of Progress—General Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in General Surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in General Surgery which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on General Surgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Evaluation of Lower Extremity Arterial Insufficiency with an Ultrasound Flow Meter

THE DOPPLER ultrasound flow velocity meter provides a simple noninvasive technique for assessing the arterial status of an extremity. The instrument produces an audible sound which varies with the velocity of red cells passing through the narrow beam of ultrasound produced by the probe.

For quantitative evaluation blood pressure measurements are made with the cuff applied at thigh, upper calf and ankle levels. The flow probe is placed over the dorsalis pedis or the posterior tibial artery and used as a sensitive stethoscope to determine systolic pressures. The values are compared with the brachial artery pressure measured with the flow probe. The ratio of ankle to brachial pressure in normal subjects is over 1.0. Lower extremity occlusive disease produces decreased values. In patients with intermittent claudication, the average ratio is 0.6; in those with pain at rest or gangrene, ratios are below 0.3. The drop in pressure between the upper and lower leg is an indication of the level of obstruction.

Measurement of ankle pressures before and immediately after exercise yields additional information, especially in early stages of disease. After five minutes of exercise no change in ankle pressure is found in normal subjects, while in patients with intermittent claudication there is a significant drop. The amount of decrease below resting pressure and the time required for recovery are guides to the severity of obstruction.

This simple technique is useful for initial evaluation of occlusive disease, for documentation of progression and for postoperative follow-up.

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Portal Hypertension in Children

EXTRAHEPATIC PORTAL VEIN THROMBOSIS is the most common cause of portal hypertension in children. In a recent study, bleeding episodes occurred in 80 percent of patients with this disorder within the first six years of life and in more than

90 percent during childhood. In contrast to children with varices caused by cirrhosis, no children died during the first bleeding episode. Exsanguinating hemorrhage is rare even with repeated blood loss. Hypersplenism of moderate degree is common, but rarely warrants splenectomy. Medical therapy with bed rest, sedation and administration of vitamin K and vasopressin tannate (Pitressin Tannate®) will stop the blood loss in most instances. Such episodes become less common during late adolescence. Emergency operations for bleeding are rarely necessary although occasional children with persistent bleeding may require selective superior mesenteric intraarterial pitressin infusion, balloon tamponade, variceal injection with sclerosing solution, variceal ligation or gastric division; however, recurrent bleeding usually follows. Cavomesenteric and central splenorenal venous shunts are the most reliable operations to control bleeding and are successful more than 50 percent of the time. The portal and mesenteric veins are usually involved with an inflammatory process throughout most major tributaries, making shunt thrombosis common. Shunts smaller than 1 cm in diameter usually close. Unsuccessful operations are usually followed by bleeding episodes that are more severe than before operation. Patients in whom shunts are done without venographic evidence of favorable vessels for anastomosis, and patients in whom various other operations are carried out to treat portal hypertension have a higher morbidity and mortality than do patients managed without operation.

In some conditions that produce portal hypertension in childhood due to intrahepatic disease there may be a fair to good prognosis if variceal hemorrhage is controlled by a portal to systemic shunt. These conditions include posthepatitic cirrhosis, fibrosis due to chemotherapy for tumor, fibrocystic disease, congenital biliary hypoplasia, glycogen storage disease and a few other diseases. An aggressive surgical approach is recommended in these children even under the age of five years, since they frequently do not tolerate variceal hemorrhage well.

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Management of Breast Nodules

IN 1974 AND 1975 the number of breast operations increased dramatically following the highly publicized operations on the wives of the President and Vice-President of the United States. One report cited a 70 percent increase in biopsies done and a 100 percent increase in malignancies detected.

The management of single breast nodules has not changed notably. Aspiration of breast cysts as an office procedure is an accepted and useful practice. Needle or aspiration biopsy of breast masses, however, requires special expertise and acceptance by individual pathologists and should not be done routinely.

Economic and logistical factors have led several centers to favor breast biopsy done under local anesthesia as an outpatient procedure, particularly when the preoperative diagnosis is of a benign lesion. However, biopsy under general anesthesia is still the most widely approved practice, with immediate radical or modified radical mastectomy done if invasive malignancy is shown to exist. Of special aid to pathologists and surgeons for localization and study of microcalcific lesions found by mammography is having a small x-ray unit (Faxitron) located in the pathology laboratory or in the operating suite.

The use of modified radical mastectomy has gained increasingly wide acceptance in treating patients with invasive malignant lesions not contiguous with underlying muscle, there being no significant difference in long-term survival following this less radical procedure.

Local excision of breast carcinoma is not an acceptable alternative to mastectomy. A recent study has confirmed the high incidence of multicentricity (41.6 percent) in breast carcinoma. As for the problem of cancer in the second breast, "prophylactic" contralateral mastectomy has not gained acceptance.

Routine biopsy of the contralateral breast, when one breast is found to have carcinoma, has been proposed but not universally accepted. Biopsy of the contralateral breast, however, is advocated for lobular carcinoma because of the extremely high incidence of bilateralism. For lobular carcinoma *in situ* detected on biopsy, simple mastectomy of the involved breast is the treatment of choice.

Finally, early results of the National Surgical Adjuvant Breast Project have indicated some

benefit of adjuvant chemotherapy with L-phenylalanine mustard in premenopausal women in whom there is axillary node involvement. The disease-free interval in women with breast cancer receiving such therapy has been lengthened. Although studies are still in progress, consideration should be given to such adjuvant therapy in appropriate instances.

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Recent Advances in the Treatment of Skeletal and Soft Tissue Sarcomas

DESPITE MORE radical surgical treatment of patients with malignant skeletal and soft tissue sarcomas, the overall survival rates have not changed appreciably in the past 40 years. However, there have been some recent developments in the treatment of these patients that deserve emphasis.

In the local control of these tumors, there have been several very important advances made. The first is the use of wide local excision, or muscle group resection, followed by high dose radiotherapy to the tumor bed. The original work of Suit and co-workers has indicated that this significantly reduces the local recurrence rate and, in fact, in some cases allows limb salvage. The basic premise is that there is increased radiosensitivity of subclinical microscopic disease, compared with the relative radioresistance of gross residual tumor.

The second advance in the local control of sarcomas is the use of intraarterial chemotherapy with doxorubicin hydrochloride (Adriamycin®), followed by wide local excision. In several instances this has allowed more conservative operative procedures and limb salvage when the only alternative procedure would be major amputation.

However, the crucial problem in the treatment of skeletal and soft tissue sarcomas is the control of distant subclinical metastatic disease. Despite the improving local control rates, the fact remains that approximately 60 to 80 percent of these patients have died of disseminated disease shortly after surgical procedures are carried out. It is therefore evident that in such patients systemic micrometastasis must be present at the time of operation. This situation has been changed by the development of two important chemotherapeutic agents. One is the antitumor, antibiotic agent doxorubicin hydrochloride, which has been shown to be effective when used alone or in combination with other drugs in the treatment of both skeletal and soft tissue sarcomas. The second is methotrexate (administered in gram amounts and followed by rescue with citrovorum—an agent that also has been highly effective against these tumors). These agents have been shown to have at least a 50 percent effectiveness in established disease. When these drugs are used before metastasis is evident, or as an adjuvant following definitive surgical procedures, the survival rates of patients have improved greatly from less than 20 percent two-year survival to greater than 60 percent two-year survival.

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Primary Closure of Civilian Colonic Injuries

THERE HAS BEEN some controversy about how best to manage traumatic injuries to the colon. Various approaches to treatment exist, ranging from colostomy to primary repair with or without exteriorization. Recently, several authors have advocated primary closure with exteriorization for colonic injuries existing for more than six hours and primary repair for isolated colonic injuries with minimal contamination of the peritoneal cavity for those operated upon within six hours of injury. Morbidity and mortality utilizing this method have been equivalent to, and in some instances better than, other modes of treatment. Primary repair of the colon with or without exteriorization is advantageous because it reduces morbidity and length of time in hospital, and eliminates the necessity of secondary operations for colostomy closure. Garfinkle and co-workers reported a 22 percent morbidity rate associated with colostomy closure.

Criteria for primary closure are right-sided colonic injuries and penetrating left-sided injuries

with minimal contamination of the peritoneal cavity that do not require resection. At present we feel the six hour "golden" period should be observed and that primary closure is certainly questionable after that time. In addition, antibiotics should be administered immediately after injury, during operation and postoperatively to reduce morbidity and mortality. Extraperitoneal rectal wounds still require a proximal diverting colostomy and appropriate drainage. Other factors arguing against primary closure are the presence of multiple associated injuries and a poor-risk patient in whom the operation would be prolonged by primary closure. When the above criteria cannot be met, the colon should be closed and exteriorized over a glass rod if possible. This is preferable to colostomy. If an uncomplicated course ensues, the colon can be returned to the abdomen in 10 to 14 days.

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Marginal Ulcer

MARGINAL ULCERS occur in 3 to 10 percent of patients in whom operations are done for duodenal ulcer. The ulcer recurrence rate after specific operations is widely variable: 34 percent after simple gastroenterostomy, 2.5 to 25 percent after vagotomy and pyloroplasty, 0.5 to 15 percent after gastric resection, and 0 to 1.8 percent following vagotomy and gastric resection. Most ulcers occur within two years of the initial procedure although the interval may be longer following gastroenterostomy.

Incomplete vagotomy is the most common cause of marginal ulcer, but other important etiological factors include retained antral mucosa following Billroth II gastric resection, unrecognized hyperparathyroidism and hypergastrinemia (Zollinger-Ellison syndrome). Clinical features of a marginal ulcer include pain (especially when located in the left upper quadrant), occult bleeding and sudden weight loss. Diagnostic tests should include endoscopy, barium upper gastrointestinal series, determination of basal acid secretion and serum calcium and gastrin determinations. A technetium scan may be useful if retained antral mucosa is suspected.

Surgical treatment of marginal ulcers is recommended and consists of completing the vagotomy and resecting the distal portion of the stomach if that has not been done previously. If hyperparathyroidism is present, it should be treated before further gastric procedures because parathyroidectomy alone may cure the marginal ulcer. A total gastrectomy should be done if hypergastrinemia is present because it is the most effective treatment for Zollinger-Ellison syndrome.

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Diagnosis of Venous Thrombosis—A 1976 Update

ALTHOUGH NEWER and noninvasive methods for venous thrombosis detection are available, radiographic phlebography is still the standard procedure for definitive diagnosis of clinically significant venous thrombosis. Indications for other procedures derive from contraindications to and impracticality of radiographic phlebography.

Noninvasive methods, including Doppler ultrasound flow detection, electric impedance and strain gauge plethysmography are adequate for detection of complete obstruction of the femoral and popliteal veins. Detection of nonobstructive, mural thrombi is less reliable, and thrombosis limited to the calf veins may not be detected with these procedures. Noninvasive thrombosis detection may be used in pregnant patients, patients with allergy to contrast media and those refusing invasive procedures.

Radionuclide angiography requires intravenous isotope injection distal to the thrombosis site. It shows the anatomy of the venous system but the quality of images is in general inferior to those of radiographic phlebography. Therefore, indications for its use are limited to patients with contraindications to phlebography. Venous scan with large radiolabeled particles (^{99m}Tc albumin aggregated) is based on Anger Camera imaging and subsequent polaroid photography of images produced by labeled particle entrapment on clots after distal intravenous radionuclide particle injection. Leg veins, iliac veins, inferior vena cava

and lungs can be scanned simultaneously and this method is adequate for screening purposes and for definitive diagnosis when radiographic phlebography cannot be done.

Serial labeled fibrinogen uptake test utilizing ^{125}I-fibrinogen is available for detection of active thrombus formation. It is the method of choice for detection of active thromboses in patients with a history of venous disease and equivocal clinical signs of activity. It has also been used for monitoring the adequacy of anticoagulation therapy. Its safety in pregnant women has not yet been shown, nor does it differentiate between superficial and deep venous thrombosis or between intravascular and extravascular fibrin deposits. Consequently, phlebography or venous scan should be done in these instances to determine the exact location of fibrin deposits detected by the fibrinogen uptake test. No instances of hepatitis following the use of the test have been reported in the United States but two instances of hepatitis have been reported in Europe, and caution is advised when other than autologous fibrinogen is utilized.

In conclusion, the newer methods for thrombosis detection complement previously existing methods. Adequate knowledge of the indications and limitations of each will result in improved diagnosis and care for patients with venous thrombosis.

ERICK W. POLLAK, MD

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Noninvasive Methods of Evaluating Carotid Circulation

THE INCREASING EFFECTIVENESS of both medical and surgical therapy in the prevention of stroke from extracranial cerebrovascular disease has given impetus to the development of simple, safe and reliable tests for assessing disease in the carotid vessels as a part of the general examination of patients at risk for stroke. The Doppler ophthalmic test and ocular pneumoplethysmography have through an accumulation and dissemination of experience proved to be of significant clinical usefulness in evaluating cases of patients with an asymptomatic carotid bruit, an episode of transient cerebral ischemia or other manifestations of cerebrovascular disease, or those in which cerebrovascular disease is suspected. The Doppler ophthalmic test identifies the presence of external carotid artery collaterals found to occur in more than 80 percent of patients with hemodynamically significant lesions of the internal carotid artery. This test requires only a relatively inexpensive Doppler ultrasonic flowmeter, and some familiarity with its use. The ocular pneumoplethysmograph measures central retinal artery pressure, as a reflection of internal carotid artery pressure, by using a sensitive transducer connected with tubing to the sclerae by a standard vacuum pressure.

Using these techniques, a physician can reliably evaluate the need for arteriography and can establish the appropriateness of a trial of antiplatelet medication (such as acetylsalicylic acid, dipyridamole, sulfinpyrazone) or the advisability of proceeding with operative therapy.

HERBERT I. MACHLEDER, MD

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Pancreatic Ascites

PANCREATIC ASCITES refers to the clinical entity in which there is massive ascites due to nonmalignant pancreatic disease. The cause of the pancreatic disease is alcoholism in most patients. The other common cause is blunt abdominal trauma, especially in children. The patient characteristically presents with recent weight loss, increasing abdominal girth and weakness. Most have some abdominal pain, mild or severe, but others have no pain. There may or may not be a history of acute pancreatitis before the onset of ascites. Typically these patients have ascites that responds poorly to salt restriction-diuretic regimens.

On physical examination, the typical patient appears chronically ill and evidence of recent weight loss and pronounced ascites is noted. The abdomen is generally not tender. Skin lesions resembling erythema nodosum may be found. They represent subcutaneous fat necrosis. Differential diagnoses include ascites due to cirrhosis, abdominal carcinomatosis and tuberculous peritonitis. Diagnosis depends on a high index of suspicion of the condition in patients with ascites, and a diagnostic paracentesis for fluid analysis. The ascitic fluid protein in cirrhosis is generally less than 2 grams per 100 ml, whereas in patients with pancreatic ascites it is frequently over 3

grams per 100 ml. The amylase content of the ascitic fluid is elevated. Biopsy of the skin lesion may help in making the diagnosis. All the pathophysiologic mechanisms involved in the formation of pancreatic ascites are not known. In some patients, there may be pseudocysts or disruption of the pancreatic duct.

If the patient is stable, medical therapy should be tried for a few weeks. Treatment is based on "resting" the pancreas and giving good nutritional support by elemental diet or parenteral hyperalimentation. Spontaneous resolution of the pancreatic ascites occurs in many patients. If there is clinical deterioration or if the ascites does not resolve, operation is indicated Pancreatography at operation or endoscopic retrograde pancreatography just before operation should be done to help determine appropriate therapy. Surgical alternatives include resection or internal drainage of the pseudocyst or the ruptured pancreatic duct. In poor-risk patients external drainage may be the initial procedure. The diagnosis of pancreatic ascites is important because in some patients operative therapy is specific and often curative.

S. Kohatsu, MD

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The Continent Ileostomy

The development of an internal ileal reservoir following total proctocolectomy was described by Kock in 1969. Full continence was not achieved until Kock constructed a valve by intussuscepting a nipple of the efferent limb of the ileal reservoir. The pouch requires roughly 40 cm of the distal ileum and exits at skin level on the abdominal wall. It is catheterized three to four times daily following recovery from operation and gradually increases its capacity to 500 ml or more after three to four weeks.

Experience in this country attests to the effectiveness of the continent ileostomy and to its widespread acceptance by patients when it functions properly. The contraindications to primary construction of this reservoir include patients with Crohn's disease of the colon and patients with ulcerative colitis requiring emergency intervention for hemorrhage, sepsis or toxic megacolon. Early complications include suture line leakage and difficulties in catheterizing the pouch due to malalignment of the exiting efferent limb. Late complications include peristomal fistula formation and loss of continence due to reduction of the intussuscepted nipple valve because of inadequate fixation.

Although the experience to date in this country is somewhat limited, there is considerable demand from patients with conventional ileostomies to have a continent ileostomy constructed. Although our limited experience verifies this trend, it also stresses the importance of the procedure being done only by those surgeons competent in gastrointestinal surgical procedures.

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Hepatic Tumor, Hemoperitoneum and Oral Contraceptives

Within the past year there has been a growing number of British and American reports of benign hepatic neoplasms developing in young women taking oral contraceptives. In many instances, rupture of the tumor with sometimes fatal intraperitoneal hemorrhage has been the first clinical event. However, upper abdominal pain, often incorrectly attributed to gall bladder disease, has been the most prominent symptom. An upper abdominal mass may be present.

These symptoms and findings in the fourth decade in a patient taking oral contraceptives should alert a physician to the possibility of this lesion. Liver function tests are not diagnostic and the alpha-fetoprotein determination has been consistently negative. Hepatic scan, sonography and selective angiography may be helpful in establishing the diagnosis before operation.

The natural history of the lesion is not known. Lesions usually are solitary but multiple nodules have been observed. The lesion is apparently benign, and many different pathologic diagnoses (including hepatic adenoma, nodular hyperplasia, hamartoma and well differentiated hepatoma) have been made and have contributed to the confusion in classification of the lesions.

In most instances, resection of the lesion by partial hepatectomy is indicated, but there is some evidence suggesting that solid lesions may regress or remain stationary upon discontinuance of the pill. While a cause-and-effect relationship

with the medication has not been established, the number of cases continuing to be reported seems to support such a relationship. Other hepatic effects of these agents have been well documented. A registry of cases established by Kent and Nissen was announced in the August 1975 issue of this journal [West J Med 123:145, Aug 1975].

This entity should be considered in the differential diagnosis of any patient taking oral contraceptives in whom there are upper abdominal symptoms, or findings consistent with hemoperitoneum. Emergency operation to control bleeding may be mandatory.

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Evaluation of Thyroid Nodules

THE MAIN REASON thyroid nodules are of concern to patients and clinicians is the possibility of thyroid malignancy. Certain conditions—such as a history of radiation exposure, especially in childhood, or the finding on physical examination of a hard discrete nodule or palpable cervical nodes—suggest that a thyroid nodule is malignant. Radioiodine scanning is the most important laboratory procedure for evaluating thyroid lesions since the information obtained helps in differentiating between multinodular goiter and solitary thyroid nodules, and also distinguishes between active, "warm or hot" nodules or inactive "cool or cold" nodules. The reason this is important is that thyroid cancer is infrequent in multinodular goiters and rare in "active" thyroid nodules but occurs in about 25 percent of patients with solitary cold thyroid nodules. Numerous other isotopic studies (including those using technetium, cesium, gallium and selenomethionine) have been used to differentiate between benign and malignant thyroid tumors but the results of these studies are not reliable enough for selection of appropriate treatment.

The recent use of ultrasound in evaluating thyroid nodules, however, seems encouraging since cystic thyroid nodules are rarely malignant. Approximately 20 percent of cold solitary thyroid tumors are cystic and aspiration of these cysts usually results in cure. We would recommend that routine evaluation of patients with solitary thyroid nodules include both radioiodine scanning and ultrasound. When cysts are present they should be treated by aspiration and suppression of thyroid stimulating hormone with exogenous thyroid hormone. One might question carrying out needle biopsy in all thyroid nodules. The main problem with biopsy is that the specimen obtained is often unrepresentative of the most important histologic status of the gland.

Two new tests that are useful adjuncts in diagnosing thyroid cancer are serum calcitonin and thyroglobulin radioimmunoassays. Medullary carcinoma of the thyroid can now be diagnosed in family members of patients with Sipple's syndrome, by determining basal and calcium or pentagastrin stimulated levels of serum calcitonin, before this tumor is clinically apparent. Serum thyroglobulin levels, in contrast, are often elevated in patients with differentiated thyroid cancer but not in patients with medullary thyroid cancer. The latter test is especially useful in following patients in whom operations for differentiated thyroid cancer have been done.

A careful history, physical examination and intelligent use of laboratory tests will help in the selection of patients who require and who will benefit from thyroidectomy. Thyroidectomy carried out by surgeons experienced in endocrine surgical operations is associated with minimal morbidity and rare mortality.

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Parietal Cell Vagotomy

IN THE PAST five years a new operation, parietal cell vagotomy, has been given a rather extensive trial in several surgical units in the treatment of duodenal ulcer disease. Although conclusions as to its effectiveness must still be regarded as tentative, the continued success of this operation as reported by those with the greatest experience is increasingly significant.

Parietal cell vagotomy consists of vagally denervating the proximal two thirds of the stomach, the site of acid production. The vagal innervation to the antrum, which travels along the lesser curvature in the nerves of latarjet, is deliberately spared so as not to interfere with vagal control

of antral motility. The major advantage of this procedure is that gastric emptying of solids remains normal and the need for pyloroplastry or gastroenterostomy is avoided. The clinical consequence is the virtual absence after parietal cell vagotomy of dumping and postvagotomy diarrhea.

The question still in need of a final answer is how effective is parietal cell vagotomy in curing peptic ulcer disease. The preliminary reports on the incidence of persistent ulcer vary widely from over 20 percent to as little as 1 percent. The latter figure represents the experience of the group at Leeds with 300 patients followed for over six years after operation. In two randomized controlled trials recurrent ulcer after parietal cell vagotomy (2 to 7 percent) was as low as after selective (total gastric) vagotomy with a drainage procedure (2 to 5 percent). It is impossible to be certain why the failure rate has been so much higher in some units than others but there are several important technical aspects of the operation that could be responsible and perhaps with greater experience the frequency of this complication can be reduced throughout.

Results of studies of gastric acid secretion after parietal cell vagotomy show a reduction in basal output of 80 percent and in maximal (pentagastrin or histamine-stimulated) output of about 50 percent. The effect has been shown to persist for as long as five years postoperatively. Three separate reports have shown that there is no relation between preoperative levels of acid secretion and the likelihood of recurrent ulcer.

Although parietal cell vagotomy has mainly been used for the elective treatment of duodenal ulcer, it has also been tried to a lesser extent for gastric ulcer and for duodenal ulcer complicated by bleeding, perforation or obstruction. The preliminary results in these special situations are surprisingly good but much more work must be done before any judgment can be made.

In summary, parietal cell vagotomy may well be as effective as truncal vagotomy plus pyloroplasty in the treatment of duodenal ulcer and it avoids dumping and diarrhea, each of which is incapacitating in about 1 percent of patients treated by the latter technique. If these favorable results can be duplicated by surgeons generally, parietal cell vagotomy may eventually be regarded as the best operation for duodenal ulcer.

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ADVISORY PANEL TO THE SECTION ON GENERAL SURGERY

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CORRECTION

In the epitome entitled "Valium® in the Treatment of Status Epilepticus in Childhood" by Bruce O. Berg, MD, which appeared in the January issue on pages 47 and 48, a mistake has been noted in the fourth paragraph. The third sentence of that paragraph should read "Respiratory arrest has been reported during the intravenous administration of Valium, and the drug should be administered slowly and in circumstances where resuscitative emergencies can be reliably handled." A clerical error resulted in the sentence stating that "Respiratory arrest has been reported during the fourth administration of Valium . . . . "

EDITORIALS

On Extending Patient Care with Physician Extenders

TWO ARTICLES appearing elsewhere in this issue address the subject of physician's assistants, or physician extenders. Both are informative and deal with the all-important relationships between practicing physicians and this relatively new kind of health professional. One article focusses more on the regulation of their activities under the law, and the other more on how they may be used productively in an office practice. Both are worthy of reflection and study and together they serve admirably to introduce the subject of using these new professionals to help improve the distribution of patient care, or health care for that matter.

It is correctly assumed (although the assumption is being challenged by various sorts of would-be independent "practitioners") that patient care is what the practice of medicine is principally about, and that a physician is the professional under whose supervision patient care is rendered. If he does not render a service personally himself, the physician may cause others to do so under his direction. Based upon this correct assumption it now is being further assumed that where patient care services are inadequate or perhaps unavailable, the problem results from a maldistribution of physicians and will be solved if physicians can be induced to settle and practice in these underserviced areas. At present we are seeing enormous and expensive efforts being made to lure, cajole or even press physicians into such service. These efforts do not seem to have been very fruitful so far and the government, as is its wont, is now seeking ways to compel physicians to work at least for a designated period of time in places determined by the government to be medically underserved.

It is suggested that this second assumption—that the existence of underserved areas is due to physician maldistribution—may not be entirely correct and that simply achieving a better distribution of physicians may not be the whole answer. Underserviced areas appear to be of two principal kinds. One is usually remote and sparsely populated. The other may be either an urban or rural ghetto, usually with a greater population density and people of substantially different cultural backgrounds. Physicians, however, increasingly tend to practice in clusters, for what appear to be good and sufficient scientific and professional reasons. They also tend to emerge from their long training and educational discipline with something of a culture of their own, no matter what may have been their original ethnic or economic background. Therefore it turns out that it requires a rather large geographic area to support a viable cluster of practicing physicians if the setting is remote and sparsely populated, and a bridging of substantial cultural differences if one is speaking of what have been called urban or rural ghettos. For reasons such as these, neither the barriers of distance on the one hand nor those of differing cultures on the other are likely to be overcome by either subsidizing or forcing physicians to try practice in these areas. And this appears to be substantiated by experience to date.

An obvious solution would appear to be the development and greater use of physician extenders to enable viable clusters of physicians to bridge the distance and cultural barriers and so extend their reach to the more remote and sparsely populated areas and to the rural and urban ghettos—all admittedly underserved at present. Modern transportation and modern communications now make this possible. Another alternative, the development of so-called independent practitioners of various kinds will no doubt be tried, but this can never be truly satisfactory for many reasons. However, physician extenders, whether physician's assistants (usually men) or nurse practitioners (usually women), can and should play an important role—perhaps the most important role—in providing more care of good quality in underserved areas. This increased provision of care is achieved by extending the reach and responsibility for patient care of physicians and groups of physicians, and thereby enabling them to serve these areas. The use of physician extenders to extend patient care would seem to be a reasonable and practical approach to a problem that seems unlikely to be solved in any other way in the foreseeable future.

—MSMW

Progress in Vascular Surgery

THE PAPER "Progress in Peripheral Vascular Surgery" by M. O. Perry appearing in this issue is a scholarly and well composed "state of the art" report. It comes at the end of 25 years of an incredible expansion of knowledge pertaining to all aspects of vascular disease spearheaded to a great extent by surgeons who have concentrated their efforts in this rapidly developing field. Dr. Perry, a seasoned vascular surgeon in his own right, has been both a participant and thoughtful observer in the effort to bring the fruits of this knowledge into clinical perspective. For those who have been less close to the scene, the reading of this paper should be particularly rewarding.

The development of the means for imparting clinical acumen and surgical skill necessary to reproduce the results in the broad area of vascular surgery described by Dr. Perry is currently presenting a unique challenge to those in the field of surgical education. The problem came into focus with the realization that the standards of performance in vascular surgery in many communities have been far less than ideal and that the frequency of preventable disasters was unacceptably high. The burgeoning field had attracted many surgeons whose previous training had inadequately prepared them to meet its challenges. Although vascular reconstructive procedures were available for the management of previously untreatable diseases, many surgeons were unfamiliar with the multiple pathologic variations which they could encounter. Operations in each of the areas described by Dr. Perry require an individually tailored approach according to the immediate problem. No single operative method can be used for every patient. In this sense there is a distinct difference from many other surgical disciplines where a single technique (pyloroplasty and vagotomy, radical mastectomy, or even aortic valve replacement) is a relatively unvarying series of technical maneuvers. The ability to select the most appropriate method for vascular reconstruction requires a broad exposure to the use of all of them. Few training programs have provided the breadth and intensity of experience to give their trainees this level of surgical judgment.

Compounding the training problem is the need for learning the technical skills unique to vascular surgery. The margin of error between success and disaster is narrower than in most areas of traditional general surgery. Complications are likely to be major, resulting in limb loss, renal failure, visceral infarction or stroke depending upon the diseased artery requiring repair.

Most of the surgeons whose results Dr. Perry describes had no alternative to developing their skills by trial and error during the evolutionary period of vascular surgery. Today, however, this pathway is no longer acceptable because of its high cost in patient morbidity. Most of these surgeons would now agree that these skills should be developed under supervision before the trainee begins his practice in the community. Current standards of excellence can only be acquired by a more prolonged and intensive exposure in vascular surgery than is now available in most surgical residencies. These facts are now evident to surgical residents who wish to practice in this field as witnessed by the flood of applications to the few programs offering special fellowships in vascular surgery.

Because of wide variations in educational opportunities, the need for establishing training standards in vascular surgery is becoming clear. Once adequate levels of experience have been agreed upon, it is to be hoped that programs in general or cardiovascular surgery will be encouraged to restructure their programs to meet these standards. To provide exposure and adequate volume, it is possible that some programs will need to direct their resources toward only a select portion of their resident group. Some have already established freestanding fellowships available to applicants who have completed their general surgical training. The American Board of Surgery has created a standing committee on vascular surgery to recommend solutions to the problem of vascular surgery training. It is hoped that Dr. Perry, at some as yet uncertain future date, will be able to report progress in the delivery of the quality of surgical results which he has described in his report.

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A BICENTENNIAL EDITORIAL

The Growing Dimensions of Personal Injury Liability

It is now just about a year since the medical malpractice crisis suddenly became evident. Its coming had been predictable for more than a decade, but to most people it seemed to arrive with great suddenness—almost as a bolt out of the blue. A major reason it came when it did was because professional liability insurance carriers had determined that the financial base provided by physicans' insurance premiums was nowhere nearly large enough to cover the escalating costs resulting from more claims, more litigation and mounting awards against defendant physicians. They reacted by tripling or quadrupling their premiums or by attempting to withdraw entirely from the field. The initial response by physicians was predictable and understandable. Anger, frustration and confusion became widespread as many physicians found themselves unwilling or actually unable to pay the new and often exorbitant premiums—or not able to get insurance at all. There was an almost desperate search for a quick and easy remedy, but even after a year none has been found. It is now becoming evident that the professional liability situation of physicians is only a tiny tip of what must be a huge iceberg of a problem which seems destined to have enormous impact on the nation as a whole as it enters into its third hundred years.

It now appears that the medical malpractice crisis is only symptomatic of the real issues to be faced—the growing dimensions of personal injury liability and the hard fact that not only physicians but sooner or later the nation as a whole will simply not be able to pay the ever mounting costs of personal injury liability if today's trends continue. This is a sobering prospect and one to give pause. The crisis first came to general attention in medicine only because the relatively small number of physicians could provide only a relatively small financial base for their professional liability insurance coverage, and this has proved entirely inadequate to meet the escalating costs of more claims, more litigation and mounting awards against physician defendants. But physicians are not alone. Many other professions are now being threatened with like problems. And similar writing is on the wall for many businesses and industries, including the insurance industry itself. If present trends continue, the dimensions of personal injury liability will eventually threaten the social and economic stability not only of medicine but of many other professions, and business and industry as well.

In retrospect the idea that a person should be entitled to receive compensation, usually money, for any misfortune beyond his control has been gaining force in America ever since the turn of the century. During this time there has been a gradual shift from a more materialistic (laissez-faire) society to a more social or person-oriented (no risk) society. This has been accompanied by a growing litigiousness on the part of the public as a whole. As this has occurred the idea of entitlement to compensation for personal injury, which is ever more broadly defined, has become deeply entrenched and indeed part of the American way of life. This will not change easily.

How then can the costs be contained, or reduced? The experience to date is anything but reassuring. Nothing which has been tried so far seems likely to significantly reduce costs. The workman's compensation approach has served to limit excessive awards but has encouraged rather than discouraged the prolongation of disability, and this has added greatly to the total cost. No-fault insurance is being tried in the field of automobile injuries (whether to person or car) and while initially it seemed to reduce costs, more experience seems to suggest that the number of claims tends to increase and there is little real incentive to reduce costs. In fact the total costs of no-fault seem to be increasing. Many are confident that arbitration will solve the problem. This would reduce some of the costs of litigation and be a speedier process, but what is often forgotten is that arbitration in fact only provides for the decision to be made by a third party who may not necessarily have any interest in the long-range impact of the cost thereof. Actually, surprising as it may be to some, there is evidence to suggest that a jury is more apt to take a "hard line" than is any other of these mechanisms for settling personal injury liability disputes, in fact this is said to happen more often than not. Nonetheless, juries have certainly made far too many excessive and unconscionable awards which were an important cause of the present crisis in medicine. The truth of the matter is that none of the existing approaches is likely to contain, let alone reduce personal injury liability costs in the long

run. Again, this is not just a problem confronting medicine or the health care industry alone. Rather it is an insidious, progressive, creeping paralysis which will slowly and inexorably advance throughout the whole social and economic fabric of America as it enters its bicentennial year —unless something is done about it.

With the exception of some instances of personal liability for municipalities, physicians find themselves face to face with this problem well before it has reached any other profession, business or industry in anything like the same crippling proportions. It is now apparent that any real solution will require some fundamental change in the present American approach to liability and compensation for anything and everything that has come to be included under the rubric of personal injury. This will be difficult at best, and certainly it will not come about simply to satisfy a demand or clamor from any special interest group such as medicine. Yet as of today the crisis is focussed in medicine, and there is a pressing need for medicine to take some action to initiate a solution.

The House of Delegates of the California Medical Association is to be commended for recognizing the situation for what it really is, and for directing that the association promptly invite representatives of other professions, various industries and labor to join in a broadly based Commission on Tort Reform to study the problem and what should be done about it—"with all deliberate haste." Tort reform may not be all that is necessary, or even what is necessary. But if the commission performs well it should identify the problem as a broad one, penetrating deeply into the nation's fabric, and then develop steps that may be taken toward a solution. The solution should be one with which all society, including physicians, can live and also one which will address the full measure of a most serious but still largely pending national problem. If this problem is not solved, it can in time only escalate into a national crisis of truly frightening proportions—not only for medicine but for the nation as a whole.

This will be a new role for medicine, one of innovator, stimulator and catalyst in the diagnosis, treatment and prevention of what bids fair to become a serious malady of American society. It is a role that could augur well for the future.

—MSMW

The Problem of Bilateral Cancer of the Breast

ELSEWHERE IN THIS ISSUE of the JOURNAL is an article by Kruse and Wagner on bilateral breast carcinoma. Findings in a number of recent studies indicate that in 10 to 20 percent of patients with cancer of the breast, histological carcinoma can be found in the opposite breast. In cases of lobular carcinoma, a frequency as high as 54 percent has been reported. These data have come from routine biopsy of the opposite breast or by radiologic examination followed by biopsy of "suspicious shadows." Since early detection has been regarded as the sine qua non of successful treatment, removal of the opposite breast would seem to be appropriate. However, before surgeons adopt such a policy, several essential facts must be taken into consideration.

It should be noted that histologic cancer is not always biologic cancer. This is clearly evident in papillary carcinoma of the thyroid in which minute examination of the opposite lobe has shown an incidence of histologic cancer as high as 80 percent. Yet actual clinical carcinoma develops over a period of 10 to 20 years with a frequency no greater than 5 to 10 percent. The same problem relates to prostatic cancer, where autopsy studies have shown histologic changes consistent with carcinoma in 50 percent of men over the age of 50. If histologic cancer means biologic cancer a controlled clinical trial of bilateral orchiectomy in men over the age of 50 would seem to be indicated and probably could receive support from federal funding. The difficulty would be to persuade individual men, especially doctors, to enter themselves in the trial.

Returning to cancer of the breast in women, the problem is similar. Black[1] has shown that the incidence of precancerous histologic changes in patients in whom biopsy is carried out for benign lesions is far higher than the actual eventual occurrence of cancer. He has also questioned the validity of total mastectomy for lobular carcinoma *in situ* on the grounds that in most patients with carcinoma *in situ,* invasive carcinoma does not develop. Furthermore, in lobular carcinoma *in situ,* invasive carcinoma—when it does develop—appears almost as frequently on the opposite side. Finally, when carcinoma does appear in such cases, it tends to be relatively favorable. Despite

these facts there are surgeons who become so concerned about preventive therapy that they are willing to offer bilateral mastectomy to patients with lobular carcinoma *in situ*.

A radical surgical attack on "histologic carcinoma" particularly in the breast, thyroid and prostate overlooks the long-standing evidence that there is a natural resistance to cancer. Over 25 years ago the writer summarized experimental and clinical evidence indicating that there is a natural resistance to the growth of cancer[2] and such experts in the field as Donald Morton and Lewis Thomas have long maintained that such resistance may have an immunological basis.

Obviously there is no established solution but surgeons faced with the problem should consider that the actual risk of cancer developing in the opposite breast over a ten-year period varies from 2 to 10 percent in reported series.[3] The risk for the first five years is no more than 5 percent. Faced with a 90 to 95 percent chance of having no trouble in ten years, most patients will opt for observation and careful follow-up. This would seem in the present state of our uncertainty to be the proper attitude for surgeons to assume.

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CASE REPORTS

Refer to: Fye KH, Moutsopoulos H, Roe RL: Renal tubular abnormalities in a patient with lupus nephritis. West J Med 124:239-242, Mar 1976

Renal Tubular Abnormalities in a Patient with Lupus Nephritis

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THE GLOMERULAR LESIONS present in patients with systemic lupus erythematosus with nephritis have been well described. Electron-dense deposits, believed to represent complement-fixing immune complexes, occur in a granular pattern along the glomerular basement membrane and in a subendothelial position in glomerular capillaries. These deposits are assumed to be causally related to the decreased creatinine clearance that develops in lupus nephritis. The tubular defects that occur in patients with lupus renal disease, both anatomic and physiologic, have received relatively little attention in the literature. A case is reported of a patient with acute systemic lupus erythematosus in whom findings from renal biopsy studies showed deposits of electron-dense material along the peritubular basement membrane and in a subendothelial distribution in peritubular capillaries. In this patient, metabolic abnormalities were also present suggestive of renal tubular dysfunction that may have been related to these deposits.

Report of a Case

A 57-year-old black woman was admitted to San Francisco General Hospital in July 1974 because of a three-month history of anorexia, malaise, recurrent fever, night sweats, polyarthralgias, pedal edema, dull substernal chest pain and a 15 pound weight loss. Except for an episode of pneumonia in 1940, a hysterectomy-salpingo-oophorectomy in 1965, and allergies to penicillin and sulfa drugs, the medical history was unremarkable.

On admission, blood pressure was 120/76 mm of mercury and other vital signs were within normal limits. The patient was cachectic but in no distress. On examination of the eyes, bilateral early cataract formation, fundic arteriolar narrowing and a fundic drusen in the right eye were noted. Many small nontender cervical nodes were found bilaterally. Chest excursion was decreased, but no rales or rhonchi were heard. Heart sounds were normal. The liver was palpable at the right costal margin. There was no tenderness at the costovertebral angles and no tenderness, erythema or effusion at the joints.

Initial laboratory data were as follows: hematocrit reading, 37.2 percent; leukocyte count, 5,000 per cu mm with a normal differential, and platelet count 310,000 per cu mm. Urinalysis showed 3+ protein, five to ten red blood cells per high power field, five to ten leukocytes per high power field and occasional granular and cellular casts. The nonfasting blood glucose level was 167 mg per 100 ml, creatinine 1.1 mg per 100 ml and blood urea nitrogen 28 mg per 100 ml, with a creatinine clearance of 28 ml per minute (it ranged between 28 and 54 ml per minute while the patient was in hospital). The albumin to globulin ratio was 3.1:4.4, and the erythrocyte sedimentation rate was 56 mm per hour. Values for serum electrolytes, hepatic enzymes, uric acid, prothrombin time, partial thromboplastin time, fibrinogen screen and fibrin-split products were all within normal limits. On roentgenograms of the chest, biapical pleural thickening, an infiltrate in the right upper lobe and a right pleural effusion were seen. No abnormalities were noted on an electrocardiogram.

Reactions on skin tests for purified protein derivative (PPD) and mumps were initially negative, although on a second PPD test the reaction was positive to 7 mm. Thoracentesis yielded clear exudative fluid with a cell count of 122 leukocytes

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Submitted, revised, August 25, 1975.

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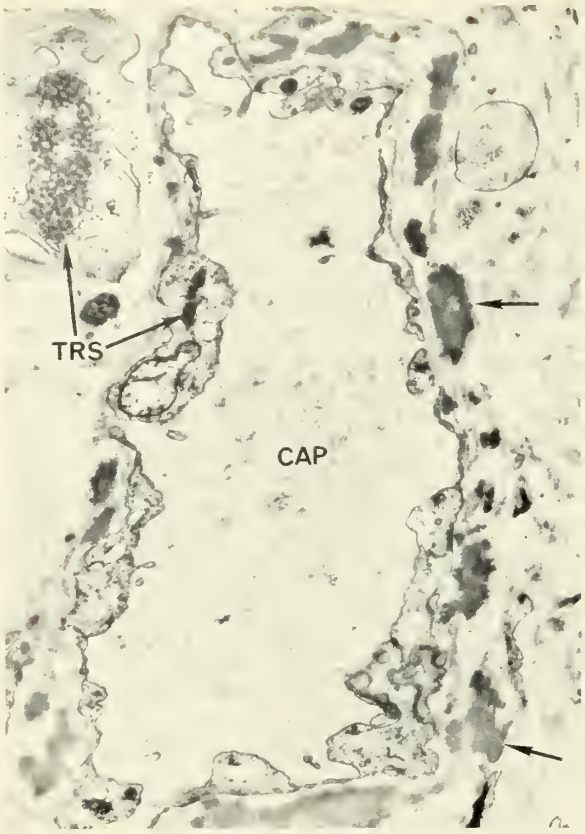

Figure 1.—Electron micrograph showing tubuloreticular structures (TRS) within the endothelial cells of a peritubular capillary (CAP). Electron-dense material is also present within the basement membrane (arrows). (Reduced from original magnification × 17,500, insert magnification × 47,900.)

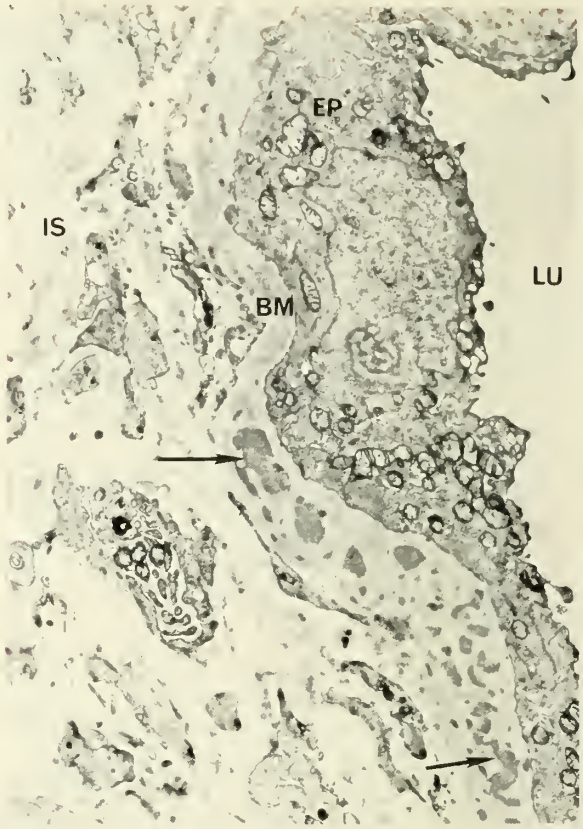

Figure 2.—Electron micrograph of a renal tubule showing the tubular lumen (LU), tubular epithelium (EP), and interstitium (IS). Electron-dense material (arrows) is seen within the basement membrane (BM). (Reduced from original magnification × 9,000.)

per cu mm (64 percent mononuclear and 36 percent polynuclear cells) and 49 red blood cells per cu mm; sputum and pleural fluid smears and cultures for acid-fast bacilli were negative. Treatment with isoniazid, 300 mg per day given orally, and ethambutol, 500 mg per day given orally, was begun.

On day 4, the temperature became elevated, and a vasculitic lesion on the right conjunctiva, muscle pain in the shoulder and pelvic girdle, and multiple arthralgias and arthritis in the right knee developed. Findings on analysis of synovial fluid included 1,130 leukocytes per cu mm (60 percent mononuclear and 40 percent polynuclear cells), 1,130 red blood cells per cu mm and a C′3 complement of 10 with a serum value of 40 mg per 100 ml. On serologic studies, findings included a positive lupus erythematosus preparation, a positive antinuclear antibody in an outline pattern (titer 1:64), a diffuse elevation of immunoglobulin G (IgG) and immunoglobulin A (IgA) fractions, and an anti-double stranded deoxyribonucleic acid (DNA) antibody titer of 517 counts per minute (normal = 150). A biopsy study of visually uninvolved skin showed immunoglobulin and complement deposition in dermal vessels.

The urinary sediment continued to reflect active glomerulonephritis and creatinine clearance remained stable at 25 ml per minute. A 24-hour urine collection yielded 1.1 grams of protein. On light microscopy of a renal biopsy specimen, focal local glomerulonephritis with endothelial and mesangial cell proliferation was noted. In some areas focal fibrosis of the involved segment of the glomerular tuft was also present. There was rare glomerular hyalinization. The tubular cells were unremarkable on light microscopy. Immunofluorescence studies showed deposits of IgG and C1q along glomerular and tubular basement membranes and in some glomerular and peritubular vessels. A few deposits of IgA and immunoglobulin M (IgM) were found in some glomerular

basement membranes and a few deposits of fibrin were present in glomerular and peritubular capillaries. Electron microscopy showed tubuloreticular structures typical of lupus erythematosus within endothelial cells in both glomerular and peritubular capillaries (Figure 1). Electron-dense material was present in subendothelial and subepithelial deposits along both glomerular and peritubular basement membranes (Figure 2). Therapy with prednisone, 60 mg per day, was begun and resulted in prompt improvement in systemic and joint symptoms although renal disease persisted.

Because a culture of urine obtained on admission showed significant numbers of Proteus mirabilis, kanamycin, 500 mg, was administered intramuscularly twice a day for seven doses. On day 14, hyperkalemia developed (6 mEq per liter) and persisted through discharge on day 54 ranging between 4.3 and 6.4 mEq per liter during sodium polystyrene sulfonate (Kayexalate®) therapy. Hyperchloremia ranging from 115 to 124 mEq per liter also developed and persisted well after therapy was begun and the levels of serum sodium ranged between 136 and 145 and bicarbonate ranged between 16 and 25 mEq per liter, respectively. These occurred without evidence of extra renal loss. Findings on urinalysis included a pH range of from 5.0 to 7.0 and intermittent glycosuria associated with blood glucose concentrations as low as 74 mg per 100 ml. Urinary 17-hydroxycorticosteroids and aldosterone levels were low (2.2 mg per 24 hours and 1.0 μg per 24 hours, respectively), but the plasma cortisol level showed a normal response to stimulation by adrenocorticotropin (from 11.0 to 32.0 micrograms per 100 ml). While the patient was on a regulated normal sodium intake, renin concentrations were low: 0.92 nanogram (ng) per ml in three hours supine (normal mean 5.5 ± 0.9 SEM) and 1.5 ng per ml in three hours erect (normal mean 13.9 ± 3.2 SEM).

Discussion

The deposition of immunoglobulin and complement along renal tubular basement membrane has been described previously. Two patterns of deposition have been shown in both human beings with disease and animal models. Steblay and Rudofsky[1] described the formation of antitubular basement membrane antibodies in guinea pigs after multiple injections of rabbit kidney basement membrane incorporated with complete Freund's adjuvant. These antibodies led to a linear pattern of proximal tubular basement membrane staining with fluorescein-labeled anti-IgG and β1C. Such linear staining along tubular basement membrane has been described for persons with Goodpasture's syndrome,[2] methicillin-associated interstitial nephritis,[3] progressive post-streptococcal glomerulonephritis[4] and human renal allografts.[5,6]

The second, or granular, pattern of immunoglobulin and complement deposition has also been observed in both human and animal tissues. Klassen and co-workers induced granular deposition of IgG along tubular basement membrane in rabbits after repeated renal allografts[7] and after repeated immunization with homologous renal tissue in complete Freund's adjuvant.[8] Klassen's group also induced granular tubular basement membrane deposition in rats immunized with homologous kidney in Freund's adjuvant.[9] They did not find circulating or fixed renal tissue antibodies that would react with normal tubular basement membrane, but they did find circulating antibodies against antigens present within the cytoplasm of proximal tubular cells. They postulated that antigen-antibody complexes diffused out of the proximal tubular cells and were deposited along the peritubular basement membrane. Granular deposits of IgG and β1C along the tubular basement membrane of proximal convoluted tubules have been observed in persons with systemic lupus erythematosus, rapidly progressive glomerulonephritis, lipoid nephrosis, and idiopathic interstitial and tubular disease.[10] Almost half the patients who have had this tubular defect have had systemic lupus erythematosus.

There have been no systematic studies correlating physiologic abnormalities with tubular deposition of immunoglobulin and complement. However, many authors have observed clinical phenomena suggestive of tubular dysfunction associated with such deposits. Klassen and associates[8] and Steblay and Rudofsky[1] documented glycosuria in animal models. Glycosuria,[2] aminoaciduria,[3] proteinuria,[2,9] hematuria[2,3,9] and a possible renal tubular acidification defect[3] have all been observed in human beings with tubular basement membrane deposition of immunoglobulin and complement. However, the patient described by Border and co-workers,[3] who was unable to acidify urine adequately even after the adminis-

tration of 7 grams of ammonium chloride, was studied after having received multiple doses of penicillin and aminoglycoside antibiotic drugs and when the serum creatinine level was 3.9 mg per 100 ml. The acidification defect might, therefore, have been due to interstitial nephritis and not tubular IgG or β1C deposition.

In our patient, electron microscopy showed pronounced granular deposition of electron-dense material along the tubular basement membrane and in a subendothelial pattern along the peritubular capillaries. Immunofluorescence proved this material was IgG, complement and fibrinogen. In our patient, the similarity of the subendothelial deposits in peritubular capillaries to those seen in the glomeruli was dramatic. Such similarity has not been emphasized previously. Tubular virus-like particles were also identified in both tubular epithelial cells and the glomeruli. Hyperchloremia, low serum bicarbonate level with a normal urinary pH and intermittent glycosuria present in our patient suggest renal tubular dysfunction. Because the juxtaglomerular apparatus was in the area involved by the tubular deposits, we raised the question of possible dysfunction of the juxtaglomerular apparatus. In our patient, there were two low 24-hour urinary aldosterone levels, resistant hyperkalemia and normal blood pressure despite the lupus nephritis. We believe she may have had transient hyporeninemic hypoaldosteronism indicative of juxtaglomerular dysfunction. Unfortunately, steroids and aminoglycosides were administered before renal tubular function and juxtaglomerular apparatus function could be evaluated adequately, and the tubular dysfunction had either responded to steroid therapy or was masked by the effects of the aminoglycosides. However, the occurrence of tubular dysfunction in patients with lupus erythematosus with peritubular deposits is likely and merits further study.

Summary

A patient with systemic lupus erythematosus and nephritis is reported in whom deposits of electron-dense material were present in glomeruli, along the peritubular basement membrane and in peritubular capillaries of a renal biopsy specimen. Hyperchloremia, a low serum bicarbonate level with a normal pH and intermittent glycosuria were noted. Transient hyporeninemic hypoaldosteronism also appeared to be present. It is likely that tubular dysfunction occurs in patients with lupus erythematosus and peritubular deposits and merits further study.

Addendum

Since our paper was submitted, peritubular deposition of immune complex material in a large group of patients has been reported (Lehman DH, Wilson CB, Dixon FJ: Extraglomerular immunoglobulin deposits in human nephritis. Am J Med 58:765-786, 1975).

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LETTERS *to the Editor*

Sudden Infant Death Syndrome

To the Editor: In his "New Perspectives in the Sudden Infant Death Syndrome" (Epitomes of Progress—Pediatrics. 124:48, January, 1976), Anders discusses the problems faced by families in which sudden infant death syndrome (SIDS) deaths have occurred. He then states, "Efforts directed toward professional and general public education, and psychological support services for families of victims are required. Parental self-help groups and professional counseling should be available."

In answer to Dr. Anders, parent groups are available. The National Foundation for Sudden Infant Death has chapters in most states. The western region includes three chapters covering California (based in San Diego, Los Angeles and Oakland) and state chapters based in Seattle, Portland, Phoenix, Reno, Denver, Salt Lake City and Albuquerque.

Professional help is also becoming available. Due to pressure from the Foundation, state and local health departments are setting up SIDS programs in many states, including Idaho and Montana. Also due to Foundation pressure, national legislation in 1974 established funding for regional programs, of which three are in the West: Washington, California and New Mexico.

The California program will serve as a backup to a legislatively mandated system passed at the instigation of the Northern California chapter. AB 409, 1974 (Crown/Lockyer) provides: (1) Mandatory autopsy, with rare exceptions, in all possible SIDS deaths; (2) if SIDS is the provisional diagnosis of the gross autopsy, the coroner must immediately notify the county health department; (3) the health department must immediately notify the family and explain SIDS to them, after consulting the infant's physician.

Norman Lewak, MD
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Northern California Chapter
National Foundation for SID
Alameda

Restrictions on Prescribing

To the Editor:

An inquiry.

Is it not curious that at a time when I see more and greater restrictions on my ability to prescribe and treat—and limits on the use of certain medications in treatment because the state and federal governments restrict my access to these medications—more and more patients now are showing me greater numbers of *over-the-counter* drugs purchased from and *prescribed* by health food proprietors. These range from inert dolomite to toxic combinations of herbs and other compounds of drugs, vitamins and cyanide from apricot pits. One woman with gallstones was even advised to see a healer in San Mateo because, she was told, medical means are not good today to treat gallstones.

Another patient informs me that she was told to chew apricot kernels daily and this would prevent cancer. They did not tell her about the possibilities of cyanide poisoning (as discussed in a recent government bulletin that came across my desk[1]).

In any case, it seems that we the professionals are being curtailed by the law that allows nonprofessionals to prescribe with no risk.

One cannot help but wonder at the law (or absence of law) that allows this. While the trend seems to be continued warranty of health from those of us licensed by the state, I see no such application to these nonprofessionals who are not licensed by the state. Those of us licensed are required to "give informed consent" to all that we do or do not do. Is this same principle applied to those who prescribe over-the-counter herbs, drugs, potions or concoctions? It seems not.

I wonder if others are concerned by this paradox. I would appreciate the views of other readers.

David A. Costanza, MD
Greenbrae, CA

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Trauma Rounds

Chief Discussant
STEVEN PARKS, MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is one of a series of Conferences on Trauma at San Francisco General Hospital

Refer to: Parks S: Inhalation injury in burn patients (Trauma Rounds). West J Med 124:244-248, Mar 1976

Inhalation Injury in Burn Patients

F. WILLIAM BLAISDELL, MD:* *The case we have selected for presentation today is a problem of inhalation injury. The case will be presented by Dr. Daniel Capen.*

DANIEL CAPEN:† The patient is an 18-year-old white man who, while under the influence of drugs, fell asleep while smoking and sustained a burn involving both arms. Apparently inhalation injury also resulted because the patient was found to be very short of breath on admission. The medical history was significant: the patient smoked two to three packs of cigarettes a day and had a chronic productive cough.

On physical examination, tachypnea and diffuse wheezes throughout the chest were noted. A 20 percent second and third degree burn of both arms and axillae was apparent.

Initial determination of blood gases included an arterial oxygen pressure (Po_2) of 70 and a carbon dioxide pressure (Pco_2) of 30 mm of mercury. However, the patient became progressively more tachypneic during the course of resuscitation and within an hour of admission the arterial Po_2 fell to 38 mm of mercury. An endotracheal tube was passed and positive pressure ventilation instituted. Following intubation and positive pressure ventilation, the arterial blood gases stabilized on 40 percent oxygen at an acceptable level. Frequent suctioning was required for abundant tracheobronchial secretions, which contained carbonaceous material. No abnormalities were seen on an initial x-ray film of the chest. On subsequent x-ray studies of the chest the progressive development of infiltrates in both lung fields was seen over a period of 24 to 48 hours.

During the next two to three days, values on determinations of blood gases gradually improved and pulmonary infiltrates cleared sufficiently so that the patient was extubated on the fifth day after injury. The respiratory course during the subsequent eight to ten days was complicated by abundant pulmonary secretions which the patient expelled with some difficulty. At the end of this time, respiratory function had returned to normal levels and treatment involved only the routine management of the burns.

STEVEN PARKS, MD:‡ This patient's burns were the least of his problems. He could have recovered sufficiently to be managed out of the hospital relatively promptly had it not been for the inhalation injury.

In the past—20 to 30 years ago—most patients with major burns died because of burn shock.

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Sponsored by the American College of Surgeons Northern California Trauma Committee. Supported in part by NIH Grant GM18470.
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TABLE 1.—*Carbon Monoxide Poisoning and Carboxyhemoglobin Levels*

Carboxyhemoglobin Level (Percent)	*Severity*	*Symptoms*
20	Mild	Headache, mild dyspnea, visual changes, confusion
20-40	Moderate	Irritability, diminished judgment, dim vision, nausea, fatigability
40-60	Severe	Hallucinations, confusion, ataxia, collapse, coma
60	Fatal	....

TABLE 2.—*Sources of Noxious Chemicals in Smoke*

Compound	*Noxious Products of Combustion*
Polyethylene, polypropylene	Clean burning, combustion to carbon dioxide and water
Polystyrene	Copious thick black soot and smoke—carbon dioxide and water, some carbon monoxide
Wood, cotton	Aldehydes (acrolein)
Polyvinylchloride	Hydrochloric acid
Nitrogen containing compounds, acrylonitrile, polyurethane	Hydrogen cyanide
Fire retardants frequently produce toxic fumes	Halogens (chlorine, bromine, fluorine), ammonia

Once the mechanism of burn shock was understood and combated with appropriate fluids and monitoring this no longer remained a major clinical problem. The next major cause of mortality was sepsis in the burn wound. However, in the last ten years the development of local therapy for burn wounds (such as silver nitrate, sulfamylon or silver sulfadiazine) has produced a pronounced drop in deaths from wound sepsis. As a result we have been left with respiratory failure as the commonest cause of death. This problem can develop at any time in the course of management. The pulmonary complication rate in most burn units is between 20 and 25 percent with 70 to 85 percent of patients ultimately dying of respiratory failure.

There are many different causes of respiratory insufficiency in burn patients. These include inhalation injury and bacterial pneumonia as the commonest, the latter being the principal late cause of death. Other types of respiratory failure which can occur less commonly include acute pulmonary edema from fluid overload, aspiration pneumonia, pulmonary embolism and the respiratory distress syndrome—which follows all those types of trauma in which there has been shock and extensive soft tissue injury.

Inhalation injury, which I will concentrate on today can produce three different types of problems, all of which are manifest in the immediate postburn period. These are inhalation of heat, inhalation of carbon monoxide and inhalation of noxious chemicals. The heat injury produces damage to the upper air passages only and rarely affects the airway below the level of the larynx. The critical problem is laryngeal edema which can lead to rapid deterioration and prompt death, if not treated vigorously. The initial manifestation of laryngeal injury is stridor. When the airway obstruction becomes critical, immediate access to the airway is indicated by intubation or, if this is difficult, by immediate tracheostomy.

Carbon monoxide poisoning is the second thing you must look for in any case of smoke inhalation. The normal carboxyhemoglobin level of blood is less that 1 percent unless the patient is a smoker in which case it may be 5 to 10 percent. Any carboxyhemoglobin level greater than 10 percent is definitely abnormal, 20 percent is serious and 60 percent is usually fatal (See Table 1). In most cases of smoke inhalation, carboxyhemoglobin levels are between 15 and 25 percent. It is relatively rare for us to see levels higher than this because higher concentrations are usually lethal at the time of the burn. This is the major immediate cause of death in patients injured in fires. Short of lethality, levels greater then 30 percent alter consciousness and lead to confusion or coma. For this reason, when a burn patient is first seen it is appropriate to start administration of 100 percent oxygen immediately and check carboxyhemoglobin levels as soon as possible. The half-life of carboxyhemoglobin is about four hours breathing room air. It is about 30 minutes when the patient breathes 100 percent oxygen. This emphasizes the importance of administering oxygen in these patients without waiting for verification of carbon monoxide poisoning.

Smoke inhalation usually is associated with inhalation of noxious chemicals. These chemicals are produced by the combustion of cotton, wood and especially plastics such as polyurethane and polyvinyl chloride (See Table 2). These toxic substances are oxides of sulfur and nitrogen, hydrochloric and hydrocyanic acids, and various alde-

hydes. Acrolein is an aldehyde produced in high quantities in wood smoke. Ten parts per million of acrolein will produce blatant pulmonary edema. This pulmonary edema results from a combination of chemical damage to the tracheal mucosa, and outpouring of fluid from alveolar irritation. When these chemicals are inspired, ciliary action and mucous transport are immediately depressed. In addition, there is peribronchiolar edema which produces obstruction of small airways. Clinically, this is indicated by wheezing. There may be sloughing of the tracheobronchial mucosa and thick chunks of mucosa may be coughed up which represent actual casts of the lower airway. The patient presented today actually coughed up bronchial casts which included recognizable bifurcations of bronchi. The end result of this complication is usually bronchopneumonia, which is the ultimate cause of death in these patients. The mortality for inhalation injury of the tracheobronchial tree may be as high as 85 percent.

In the patient discussed today there was a chemical tracheobronchitis with peribronchial edema which produced obstruction of the small airways. This caused hypoxia until positive pressure ventilation and administration of increased concentrations of oxygen were undertaken. It was remarkable that the patient recovered rapidly enough for use of a ventilator to be discontinued in five days but it was ten days before recovery to the preburn state. Thermal injury of the upper airway was also present, as shown by the development of a granuloma on one of the vocal cords.

I would like to emphasize that in any case in which there is evidence of singed hairs on the patient's face, eyebrows or hairs of the nose, or burns about the face, there is possibility of inhalation injury even though initial findings on respiratory examination are normal. Patients must be examined at frequent intervals. Shortly after the onset of rales, wheezing or stridor, the patient's course may be rapidly downhill and he may become hypoxic and require emergency intubation. Frequent and repeated physical examinations will give the earliest reliable signs of impending trouble.

Charles Blakely, MD:* We did not obtain a carboxyhemoglobin level in this patient at the time of admission, but two hours later, after 100 percent oxygen had been administered, there was a carboxyhemoglobin level of 16 percent. In addition, I carried out a bronchoscopic examination immediately after admission. The airway was found to be slightly erythematous, but the magnitude of the injury was underestimated. The extent of damage to the upper airway was not fully evident until several days later. One of the reasons for this was that bronchoscopic examination was done immediately after the patient's arrival and it is probable that sufficient time had not elapsed for the full extent of the injury to be recognized.

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Dr. Parks: I believe that in all patients who have evidence of inhalation injury, even mild, fiberoptic bronchoscopy should be done as part of initial assessment at the time of admission. In several series this has been done routinely and it has been shown that possible difficulties can be anticipated rather than waiting for respiratory obstruction or a fall in arterial blood oxygen tension to develop. Erythema and early edema of the larynx and trachea are evidence that inhalation injury has been sustained. Intubation and positive pressure ventilation must be carried out immediately if survival rates are to be improved and complications reduced in such cases.

We use nasotracheal and orotracheal tubes for the initial resuscitation. This is definitive in most patients. In some of the major inhalation injuries, there may be enough mucosal damage so that it is difficult to keep a patient's tracheobronchial tree clear. Although we have preferred to avoid tracheostomy as part of initial management, under these circumstances tracheostomy may be indicated. Tracheostomy is also indicated in other circumstances in which there has been severe upper airway damage with acute laryngeal edema. Those inexperienced with intubation probably should do an immediate tracheostomy rather than attempt to place a tube when respiratory distress develops.

Dr. Blaisdell: *How do you carry out emergency tracheostomy, Dr. Parks?*

Dr. Parks: If you have good light and good exposure and the patient is not in distress, you can do a conventional tracheostomy at the level of the second or third tracheal ring using a transverse incision. If the patient is short of breath or the problem is very urgent, you can do a coniotomy, even with a penknife if necessary. The cricothyroid membrane is easily located by palpation of the extended neck. The thyroid cartilage can be felt and the defect between it and the cricoid cartilage can be easily opened with one transverse

motion of the knife. It is important, however, to control the knife so that the posterior wall of the trachea is not injured with the initial thrust of the knife. Bleeding is usually negligible as this is an avascular area. An endotracheal tube can be inserted rapidly and control of the airway obtained. This technique can be used for any patient in whom an extremely urgent airway problem is present, including someone who has aspirated foreign material as a result of loss of consciousness. Later, preferably within 24 hours, this should be converted to a conventional tracheostomy.

At San Francisco General Hospital we rarely use emergency tracheostomy because anesthesia expertise is readily available, 24 hours a day. In other hospitals, however, tracheostomy may frequently be indicated. The only problem is that this results in earlier contamination of the airway because the raw tracheostomy wound often heals poorly in critically injured patients and allows contamination of the lower airway. Orotracheal or nasotracheal intubation seems to be associated with a cleaner airway for a longer time.

Our anesthesiologists use sedation, a small dose of curare followed by succinylcholine, and can intubate the agitated patient readily in this fashion. However, one has to be expert in the use of these drugs and I would not advoeate this technique for use by the inexperienced.

DR. BLAISDELL: It should be remembered that in a patient who comes in off the street, and who has not been given oxygen and has been breathing ambient air, the administration of 100 percent oxygen by mask usually improves the situation immediately. This permits plenty of time to obtain control of the airway in a conventional fashion.

A PHYSICIAN: *What is the role of steroids in the management of acute airway injury?*

DR. PARKS: Pediatricians have considerable experience with the use of steroids in acute inflammatory airway edema. Edema in burns, however, will not go away with steroid therapy. Such edema is a burn injury as opposed to an infectious injury. While the wheezing from peribronchiolar edema is similar to asthma, it is a chemical injury which is not reversed by steroids. We have tried aminophylline and the other agents used in asthma to treat this type of wheezing but it is not very successful. Bronchodilators do not resolve peribronchiolar edema or mucous plugs but may reduce associated bronchospasm.

Beyond this, steroids are contraindicated in burns because they decrease resistance to infection. Dressler, in a number of experimental studies in animals, found that mortality was increased dramatically in the group of animals that had experimental burns treated with steroids. Although in the animals temporary improvement was achieved using steroids, mortality was doubled in 72 hours. Therefore, I believe that steroids are contraindicated in inhalation injury.

A PHYSICIAN: *Does positive pressure ventilation have any direct role to play besides creating a closed system and increasing the concentration of oxygen?*

DR. PARKS: In several series, one of the remarkable things noted was that positive airway pressure controls the edema. The opposite of this is the observation that creation of a tracheostomy without utilizing positive pressure removes the ability to generate a positive pressure and cough. This has resulted in rapid deterioration and outpouring of pulmonary edema in a number of patients.

Positive pressure ventilation maintains patency of terminal airways and tends to keep them open, preventing progressive atelectasis. When there is any evidence of airway injury in a patient we institute positive airway pressure immediately and believe that by so doing we maintain patency of the airway.

DR. BLAISDELL: *Dr. Parks, would you comment on the effect of burn eschar on ventilation?*

DR. PARKS: Within a matter of hours after a major burn of the chest, the eschar, even though it is not circumferential, will restrict thoracic motion. The patient can become more and more hypoxic and has to work harder to breathe. When the eschar occupies a quarter or more circumference of the chest, immediate escharotomy should be carried out by making multiple longitudinal incisions in the eschar down to viable subcutaneous tissue. It has been our observation that after this is done, patients start to breathe better immediately.

JAMES HOLCROFT, MD:* Dr. Hiram Polk's studies are of interest. He produced inhalation injury in rats and attempted to cause pulmonary edema by administering large quantities of fluids. Surprisingly, he was unsuccessful in producing pulmonary edema despite a dramatic fluid overload. Therefore, the major problem in edema associated with

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inhalation injury would seem to be the direct effects on the airway of the smoke itself.

I am not sure that use of positive pressure ventilation will actually decrease the burn edema. Dr. Robert Demling has studied the effect of positive pressure ventilation on pulmonary edema. While positive pressure ventilation does maintain airway patency, and the values on determinations of blood gases improve, it does not decrease the amount of water or edema fluid in the lungs. This improvement may be the result of ventilation of more alveoli.

GEORGE SHELDON, MD:† I would like to point out that arterial Po_2 determination does not give any indication of the level of carboxyhemoglobin. So, for all practical purposes, it is best to anticipate that carboxyhemoglobin levels must be high and to maintain administration of 100 percent oxygen for one hour or longer whenever there is evidence of inhalation injury. By this time the patient's hemoglobin level should have recovered sufficiently to prevent death. This is particularly important in hospitals where carboxyhemoglobin levels cannot be obtained.

DR. PARKS: The major problem with the co-oximeter used for carboxyhemoglobin measurements is keeping it clean and ready to use. If the machine is meticulously maintained, it will give good results. It is very simple to use and anybody can learn to run it. The primary reason for measuring carboxyhemoglobin is to know when you can safely stop giving high concentrations of oxygen. We should continue to give oxygen until the carboxyhemoglobin level is below 15 percent. By so doing it is possible to avoid prolonged administration of 100 percent oxygen which in itself can produce pulmonary damage.

DR. BLAISDELL: In summary, this discussion emphasizes that if a burn patient dies soon after injury it will most likely be due to a respiratory problem. Other aspects of burn injuries such as fluid resuscitation and prevention of prolonged shock are better understood and managed.

Things can happen very quickly to the airway, as Dr. Parks emphasized, which may result in death. These include direct damage from heat and inhalation of toxic substances, including carbon monoxide. Edema of the airway can develop very rapidly and a patient can change from appearing to be relatively well to being critically anoxic in a matter of minutes. We must assess and continue to reassess the airway in a patient in the initial period following a burn sustained in a closed area. At present, as Dr. Parks has indicated, respiratory injury accounts for the largest proportion of deaths in burn patients who are being managed in sophisticated burn centers.

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Strategies for Productivity with Physician Extenders

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PRODUCTIVITY IN MEDICAL SERVICES is an issue that has gained considerable attention in recent years. Some health professionals believe that the term "productivity" connotes a factory orientation that is inappropriate to health care. Yet, the *concept*—if not the term—is implicit not only in many of the diagnoses ascribed to health care system problems but is also implied in many of the treatments being prescribed for solving those problems. Although productivity will not solve the problem of maldistribution of physicians, the concept appears particularly relevant to other issues surrounding the delivery of primary care. From the physicians' standpoint, productivity may affect income and hours worked; from society's standpoint, productivity of physicians restricts or enhances accessibility to care.

This paper focuses on the physician's office or clinic as the principal location where primary care is delivered. More specifically, it describes observed strategies for utilizing newer types of physician extenders (for example, nurse practitioners, Medex program graduates, physician associates/assistants) in physicians' offices. Our objective is to analyze those strategies to determine their implications for physician productivity. As a consequence, we suggest that the productive use of physician extenders should be viewed along a time continuum which evolves from one strategy to the next as a result of certain critical decisions made by the physician.

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Scope of Study

An Index of Productivity

The simplest measure of physician productivity is the number of patient visits that an office can serve per hour of physician time expended. As an output measure, this definition has deficiencies since important considerations such as patient mix, quality of care and physical facilities are taken as constants. Nevertheless, it has proven useful in the past as an index[1] for comparison and is adopted for this paper. Apart from the fact that no completely satisfactory alternative measure exists, this index of productivity has the advantage of being based on an important input—the time of the physician. It is this time—and the alternative ways a physician might choose to use it—to which physician extenders offer a potential contribution. To some extent, the way physicians use their own time is a direct function of how they wish their practice routines to be organized. In practices using physician extenders, practice routines are necessarily altered depending upon the particular strategy employed for utilizing physician extenders.

Review of Applicable Literature

The literature has not been explicit regarding general strategies for using physician extenders in a physician's office. It does, however, include surveys and time studies of how physicians spend their time,[2] hypotheses as to what portion of a physician's time and tasks might reasonably be allocated to physician extenders,[3] projections as to potential gains in productivity by using physician extenders in certain situations[4] and, finally, before-and-after studies suggesting actual productivity increases at between 10 and 75 percent in patient visits per physician hour.[5,6] In addition, training programs, attitude surveys and legal considerations are discussed.[7] In general, much of the literature supports the concept of physician extenders when the extenders carry out allocated functions under appropriate supervision of a physician. Most of the studies of physician extender practices have concentrated on task analysis and clinical objectives. To carry out tasks or meet objectives productively, however, some procedure must exist for routing a patient to the appropriate resource (physician or physician extender) within a physician's office. Such a procedure is required to insure that the coordinating/supervising/controlling elements of the physician-physician extender relationship occur. Arrangements must be made so that the physician extender has access to the physician for advice and assistance. These aspects of the physician-physician extender practice might be termed "the strategy for using physician extenders." Many alternative strategies might be conceived abstractly, but the approach of this study is to document the patient flow patterns in practices already experienced with physician extenders.

With respect to productivity, there are three factors in any such strategy that one might hypothesize as being particularly important: the ratio of physician extenders per physician, the number of patient appointments made directly with physician extenders and the extent to which patients are cared for in the office by a physician extender without a direct face-to-face encounter between physician and patient. (The third factor, expressed as a percentage of total patient visits to the practice, is termed "patient management delegation" in this paper.) These factors are only partally addressed in the literature. Case reports regarding physician extender practice almost invariably concern the use of one physician extender, although Uyeno[8] and others[9] have studied the design of health care teams by using mathematical models. Direct appointments are reported for nurse practitioners[10] and implied for other types of physician extenders. The concept of patient management delegation is less often addressed.

While one may interpret the data in several published studies indirectly, four references provide a range of specific data which bear directly upon the extent to which certain patient visits might be served by physician extenders without having patient-physician contact. Two of those studies were concerned with the design and evaluation of formal algorithms (or protocols) to be used by physician extenders in ambulatory care settings. Sherman, Reiffen and Kamoroff reported that, by using chronic disease protocols, minimally trained health assistants were able to handle approximately 30 percent of selected visits for follow-up care involving diabetes, hypertension and cardiovascular diseases.[11]

For patient visits involving 11 of the most common acute complaints, Sox, Sox and Tompkins reported that algorithms designed for Medex program graduates hypothetically permitted complete evaluation by these persons in 45 percent of the total visits. Among the 11 complaints, some (such as shortness of breath) could never be handled by a physician extender alone. Other complaints (such as upper respiratory infections, ear problems and lacerations) could be handled by a physician extender alone in 55 to 65 percent of the patient visits. In total, the 11 complaints were estimated to account for more than half of those seen in a general outpatient practice.[12]

The third study involved the use of nurse practitioners in general practice. In this study, nurse practitioners saw 29.9 percent of a practice's patients during the first year and 34 percent in the second year. Most of the appointments with a nurse practitioner were for routine examinations, well-baby care and complaints of a less serious nature.[13] In a study of a medical nurse practitioner in a primary care facility serving low income families, the person studied reportedly managed 39 percent of all acute visits and diagnosed and independently treated most of those patients.[14]

Site Visit Procedures

To more clearly identify alternative strategies for using physician extenders, observations were made in several sites in the eastern United States.

TABLE 1.—*General Attributes of Observed Sites*

Sample Codes	*Medical Specialty*	*Physician Extender Job Title*	*Years in Present Form of Operation*	*Location*	*Population Center Served*	*Organizational Framework*
KC ..	General adult medicine	Nurse clinician	2	Kansas City, Mo.	Urban	Teaching hospital clinic
CT ..	General adult medicine	Physician's associate	3	Cooperstown, N.Y.	Rural	Primary care clinic in hospital
NM ..	General adult medicine	Medex	1	Nashua, N.H.	Suburban	Multi-specialty group
NP ..	General pediatrics	Nurse practitioner	2	Nashua, N.H.	Suburban	Multi-specialty group
NO ..	Obstetrics/Gynecology	Nurse practitioner	2	Nashua, N.H.	Suburban	Multi-specialty group
GX ..	Family practice	Physician's assistant	1	Galax, Va.	Suburban	Partnership
SL ...	Pediatric specialist in allergy and chest problems	Nurse practitioner	1	St. Louis, Mo.	Urban	Solo practice
BC ..	Diabetic clinic	Health assistant	1	Boston, Mass.	Urban	Research clinic within a hospital
VS ...	General practice	Control site	10	Versailles, Mo.	Rural	Partnership

Basic criteria for site selection included at least one year's experience in using physician extenders with a physician available on the premises; some variety as to medical specialty, type of physician extender and organizational entity, but with an orientation toward primary care; a fee-for-service payment mechanism. Physician extender training programs and physician/researchers familiar with physician extender practices were contacted for recommended sites meeting those criteria. Eight sites using physician extenders were contacted. Each of them approved observations being made at their facility. An additional site, which did not use physician extenders, was selected to serve as a reference point for describing alternative patient flow patterns. Table 1 lists some attributes of those sites. Each site was visited for an average of three days during the summer of 1973. Each site visit included documentation of the patient flow patterns, and interviews with staff members. In five sites, at least one day each was devoted to collecting service time data. An attempt was made to analyze appointment records and other practice statistics for the purpose of estimating productivity trends. However, it was found that at none of the sites had sufficient input-output statistics been maintained to totally satisfy that purpose. To encourage cooperation from the sites, patient medical records and practice financial matters were specifically excluded from the study design.

Results of Site Visits

In the eight sites at which there was experience in using physician extenders, only three distinct patient flow patterns were observed. For clarity, these patterns are defined and labeled "series," "parallel" and "consultive." Those elements of the patterns concerning the patient-physician-physician extender interactions are shown in the flowcharts in Figures 1, 2 and 3. As a point of reference, the site which did not have physician extenders (vs) used what might be labeled the "traditional" patient flow pattern. Patients are given an appointment with a physician. When an examination room is available, a medical assistant prepares the patient for the physician; and the physician then provides the bulk of the patient care rendered.

In practices using physician extenders, some reorganization of practice routine occurs. The flowcharts shown in Figures 1, 2 and 3 employ a common terminology in order to emphasize that reorganization. The patient appointment block merely indicates the resource (a physician in the traditional pattern; a physician or a physician extender in the other patterns) with whom the patient is given an appointment. The patient entry block represents the process in which the patient is prepared to be served. It includes recognizing that the patient has arrived and is waiting, and obtaining the patient's records, the complaint or reason for the visit, vital signs and specimens for

laboratory work. In addition, the patient is placed in an examining room prepared to await the arrival of the physician or physician extender. This patient entry process typically is carried out by the office nurse or medical assistant. The block denoting patient contact with a physician or physician extender represents, in its simplest form, the variable amount of time that the resource spends with each patient in providing the required service. The communication block may represent a review of written material or a "consult" between the physician extender and the physician relative to a specific patient being treated, or both.

Two of the units (BC, GX) utilized what is defined as a "series" pattern of patient flow. This pattern, shown in Figure 1, represents the smallest divergence from the traditional patient flow pattern. The term "series" implies that all patient appointments are made with the physician and that all patients will be served by the physician regardless of whether or not the patient also is seen by the physician extender. Four units (CT, NP, NO, SL) used what is defined as a "parallel" pattern of patient flow. This pattern, shown in Figure 2, recognizes that patients are given an appointment either with the physician or the physician extender with the a priori expectation that some patients will complete their service without direct face-to-face contact with the physician. Two units (KC, NM) used what is defined as a "consultive" pattern of patient flow. This pattern, shown in Figure 3, includes several important considerations. First, all appointments to the practice unit are booked directly with the physician extender and none directly with the consulting physician. Second, several physician extenders work in conjunction with one physician whose role is primarily that of consultant to the physician extenders. Third, there is the expectation that some patients will complete their service without direct face-to-face contact with the physician. None of the observed sites kept sufficient routine statistics to permit an estimate of the patient management delegation from past data. In five sites, data from at least one day's observations were recorded during the study period to estimate this variable. Before making these observations, the physician or physician extender (or both) was asked for an estimate of the patient management delegation. The results are given in Table 2.

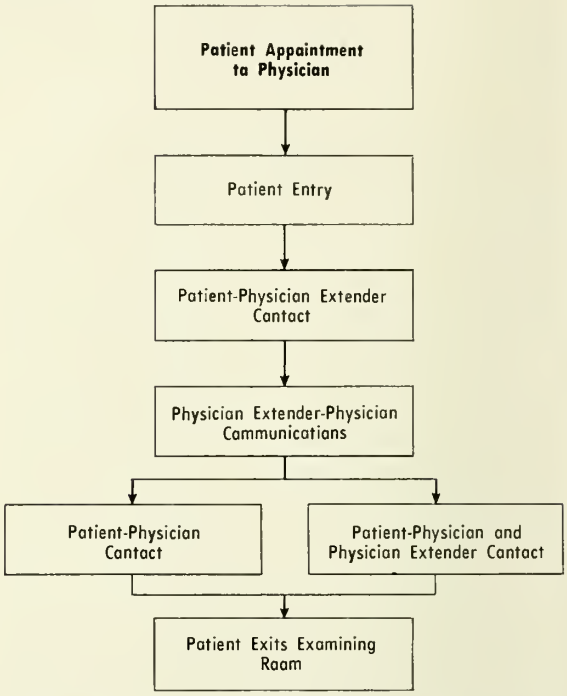

Figure 1.—Basic patient flow patterns: Series.

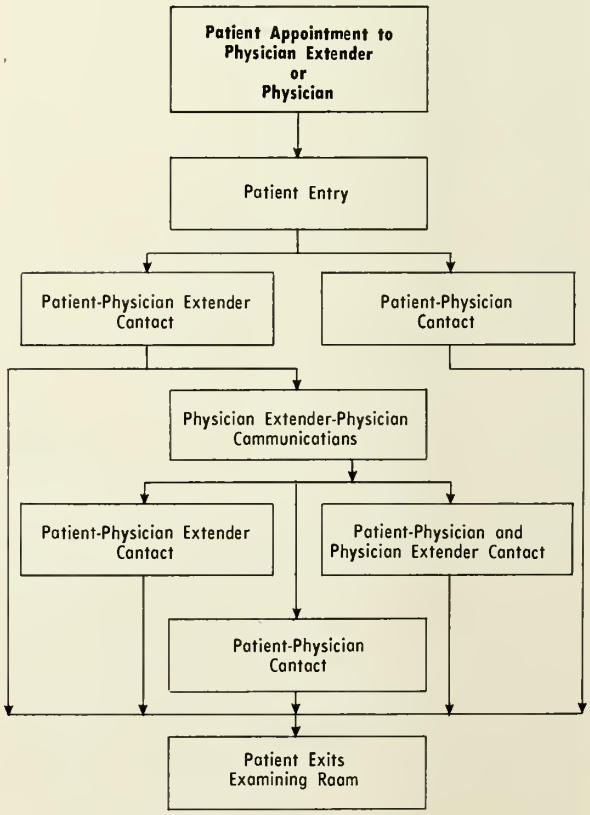

Figure 2.—Basic patient flow patterns: Parallel.

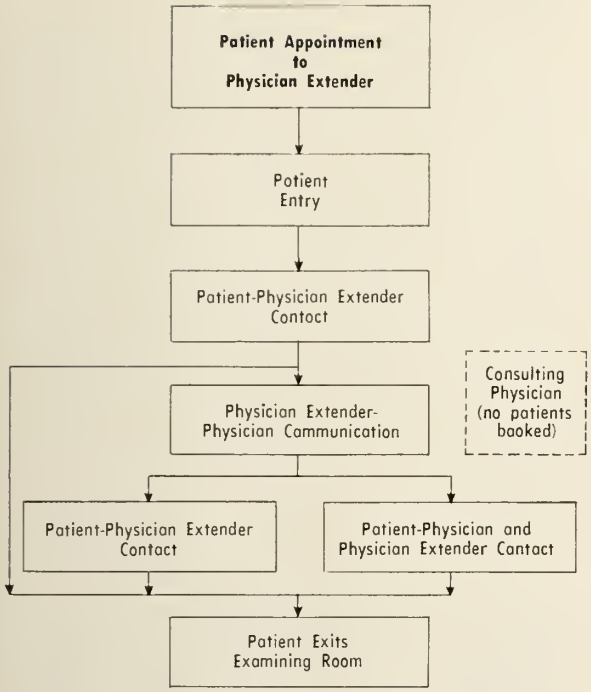

Figure 3.—Basic patient flow patterns: Consultive.

Discussion

Four Dimensions of a Strategy

In terms of strategy for using physician extenders, it is important to note that the observed patient flow patterns differ in four dimensions. First is the matter of patient appointments. The series strategy calls for appointments only with the physician while the parallel and consultive strategy permits appointments with the physician extender. Hence, a quasi-partitioning of the patient load has occurred into a portion thought suitable for the physician extender and a portion that is not. The second dimension involves patient management delegation. Once a quasi-partitioning of a patient load is permitted, there is some a priori expectation that some patient visits may be served by the physician extender without the physician having face-to-face contact with the patient. The third dimension is the number of physician extenders who work with one physician. In the observed sites, only those under the consultive strategy used more than one physician extender per physician. In those, it ranged from two to four depending upon staff scheduling for that day. The sites using the consultive strategy were multispecialty groups in which the physicians alternated days as consulting physicians to the physician extenders. The delivery of primary care

TABLE 2.—*Extent of Patient Management Delegation Judged by Patient Visits Having No Direct Patient-Physician Contact*

Basic Pattern	*Unit*	*Estimate by Unit Personnel (percent)*	*Estimate Based on Observations (percent)*	*Number of Observations*
Series	BC	0	0	20
	GX	near 0	20	82
Parallel ...	SL	<30	10	29
	CT	<50	39	18
Consultive .	NM	40-60	56	32

was the principal objective of the physician extender-consulting physician clinic.

The importance of the fourth dimension was not anticipated in advance nor does the literature indicate its importance. This dimension is the communication method that occurs between a physician extender and the physician during the process of a patient visit. In sites using the series pattern, the predominant communication method was through the patient chart. The physician reviewed the physician extender's notes before entering the examining room and following the physician extender. In the parallel and consultive patterns, the major communication method was verbal via a "consult." The consult is the mechanism through which the coordinating/supervising/controlling elements occur in the parallel and consultive patterns. In addition, this consult provides a major portion of the continuing education of the physician extender. Viewed in this context, the consult appears as the mechanism by which a physician-physician extender practice is able to adopt the dimensions of the parallel and consultive strategies. In the sites observed in this study, a consult occurred in approximately 75 percent of the patient visits in which the appointment was with the physician extender. It averaged two to three minutes per occurrence in most sites with many shorter ones (signing prescriptions, for example) and an occasional long one (typically involving some educational aspects for the physician extender). While physician time spent in a consult removes the physician from direct patient contact, it is this portion of physician time which appears to make the use of physician extenders increasingly productive.

Method for Comparing Strategies

How much more productive is one strategy than another? The question can be answered only with reference to a single practice. And with any reasonable control over experimental conditions,

the question can be answered only in the abstract by using a model. The approach chosen in this study was to develop a computer simulation model of one of the observed sites (GX) based upon data collected for 82 patient visits. The GX site was chosen as model because it was a very busy family practice in a typical small community and was only beginning to evolve beyond the simplest series pattern of patient flow. Simulation is a technique of analysis frequently useful when "real world" experimentation is impractical or when it is desirable to hold several variables fixed while one or more other variables are studied in isolation. In one form, simulation may be thought of as calculation from mathematical relationships. In an extension more appropriate to health systems studies, however, the so-called "Monte Carlo" technique is employed to generate random fluctuation. In this way, a researcher may represent in a model such essential features as variation in the amount of time that a physician may spend with a patient. Hence, a simulation model involves mathematical representations of functional relationships between system components (patients, physicians and physician extenders, for example) and data which realistically portray the variable nature of the activity that takes place within that system.

Conclusions drawn from simulation models are best viewed as tentative and subject to experimental validation in the real world. However, they frequently point to avenues of explanation and prediction for system phenomena that are difficult to identify by observation of a complex real world system in actual operation. Before comparing strategies, the model was first tested by comparing model results against observed productivity results at GX under this series strategy of operation. After reasonable congruence in both model behavior and productivity prediction was shown to exist, sets of simulation experiments were run where other physician extender strategies were imposed upon the model. The intent is to illustrate, in numerical terms, relative comparisons between typical configurations for the series, parallel, and consultive strategies. The comparisons are shown in Figure 4, where each data point is the mean of 40 simulated clinic sessions of 100 patient visits each.

Productivity Implications

Range of productivity possible—The example of Figure 4 in its traditional pattern (point T)

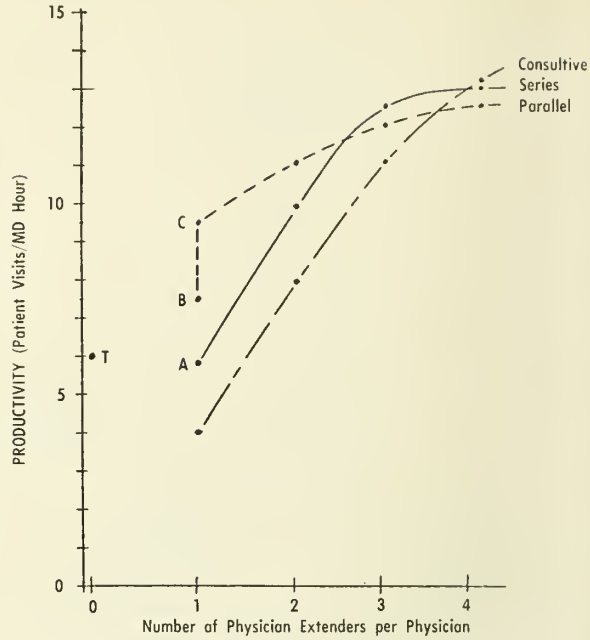

Figure 4.—Simulated comparison of physician extender strategies.

represented a high-paced family practice unit seeing an average of six patients per physician hour. In the simultation experiments, using the same pace, with one physician extender under the alternate strategies and a range of observed patient management delegation rates, the productivity ranged upward to a maximum of 9.5 patient visits per physician hour or a maximum increase of 58 percent over the traditional pattern of operation. This result, while for a single simulated practice, agrees reasonably well with the "before and after Medex" studies of Smith and coworkers,[5] which yielded productivity increases over nine practices ranging from 13.5 to 62.8 percent. It is somewhat less than the "over 70 percent" potential increase cited in a Duke University brochure regarding physician associates.[6] However, neither reference described the physician extender strategy employed in the practices although both references referred to the inconsistency of results among different settings—perhaps due to different strategies.

Sources of productivity gains—Clearly, Figure 4 suggests that a physician who employs one physician extender would gain maximum productivity from the parallel strategy. The parallel strategy has two features that are reflected in Figure 4. First, some patients are given appointments directly with the physician extender while the physician cares for the remaining patients without the physician extender being involved. This is in

contrast to the series pattern where both the physician extender and the physician see every patient *in series*. Eliminating the variable of patient management delegation, the difference in productivity between the series and parallel strategies as shown in Figure 4 is the difference between point A and point B. That is, even with a physician extender, a physician is unlikely to increase productivity over the traditional system of operation (point T) if the physician extender is used only as a more highly skilled office nurse or medical assistant. While the physician extender does absorb some physician tasks, there is a compensating effect from increased communication and coordination requirements and reduced flexibility in the use of examining rooms. Therefore, *the first source of productivity increase to be obtained by using physician extenders is derived by the quasi-partitioning of patient visits that is implicit in the parallel strategy.*

A second feature of the parallel strategy is that there is an a priori expectation that at least some of the patient visits may be served entirely by the physician extender without direct patient-physician contact. The effect of this feature is seen in Figure 4 as the difference between point B and C. Point B is the parallel pattern with no patient management delegation. Point C is the same pattern and configuration with 40 percent of the total patient visits being served by the physician extender "without direct patient-physician contact." This does not imply that the physician is not consulted by the physician extender during the patient's visit. In fact, the simulation data used to generate the results shown in Figure 4 assume (based on observed statistics) that three quarters of the patient visits served by the physician extender require a consult between physician extender and physician before the patient leaves. Therefore, *the second source of productivity increases to be obtained by using physician extenders is derived from patient management delegation.* It is to be noted that the skill of the particular physician extender is assumed to be the same throughout this analysis. Therefore, it is the strategy that reflects the sources of productivity increase in these experiments and not differing skill levels or task allocations.

Altered role of the physician—Certainly, one would expect that once a strategy is adopted that permits patient management delegation, then the extent of patient management delegation and the extent to which consults are required become primary determinants of productivity. The simulation analysis substantiates this intuitive reasoning. An important consequence of this reasoning, however, relates to the fundamental role of the physician in such an ambulatory care delivery unit. As long as the physician uses a single physician extender in the parallel strategy, the physician remains primarily a "provider of care." However, once the number of physician extenders per physician in the unit is increased, the physician's role tends toward becoming a "manager of care" or a "consultant," rather than a provider of care. This is true, regardless of the intended pattern of operation. In the particular illustration of Figure 4, the physician is forced into what is primarily a "consultant" role at the point where he uses three or four physician extenders. Beyond that point, the series and parallel strategies converge to the consultive. Then, the productivity potentials differ (as in Figure 4) only as a function of how quickly the joint roles of the physician (provider and consultant) saturate the available time. With other examples, the critical ratio will be different but the principle appears valid: *increasing use of physician extenders tends to magnify the role of the physician as a "consultant" rather than a "provider of care."*

Evolutionary Decisions Involved

Instead of viewing the series, parallel and consultive strategies as alternatives, it may provide more insight into the use of physician extenders to view them as points along a time continuum. The four dimensions defining a strategy then appear within an evolutionary context in which the series strategy would appear as a logical first step for utilizing a physician extender in a practice which heretofore had not had one. A physician extender is presumably trained and permitted to do a wider variety of tasks than can office personnel in a traditional practice setting. Many of these tasks are ones that were previously done by the physician. In addition, of course, the physician extender may do certain tasks or patient care functions that before were not provided at all or in such detail because of the demands upon the physicians' time. The actual time required for the physician extender to do such tasks may be less than, equal to or greater than the time that a physician might take. In any case, however, one strong factor implicit in the series strategy which makes it a logical first step in the utilization of a physician extender is that the physician continues

to have face-to-face contact with virtually all patients. A patient is usually first seen by the physician extender and services provided to the extent of the physician extender's current skills and abilities. Then, the patient is subsequently seen by the physician presumably for a shorter time than had the physician carried out all the services for the patient. If the physician extender is able to and does do a fairly large proportion of the total tasks for most routine office visits, then the productivity of a delivery unit operating in this series strategy is largely geared to the physician extender. Strictly followed, the series strategy offers only minimum opportunity for productivity increases since, in effect, part of the physician's time is spent waiting for the physician extender to complete tasks, in reviewing physician extender notes and findings, and in repeating a certain portion of the tasks already completed.

An early modification of the series pattern is a quasi-partitioning of patients either by the physician taking some patients immediately without sending them to the physician extender or by actually appointing certain types of complaints directly to the physician extender. In a family practice context, these complaints might be the upper respiratory infections, ear problems and lacerations which might be considered within the physician extender skill range. Even if the physician continues to see every patient (that is, when there is no patient management delegation), the system has evolved to one of the basic features of the parallel strategy and productivity is increased (by 25 percent in the practice simulation example).

In these early stages of the physician/physician extender relationship, it is to be expected that some measure of mutual trust and confidence will be developed. At some point, it will appear reasonable, safe and convenient for the physician extender to report findings verbally (in a consult) and to receive the physician's verbal approval as to the disposition of the patient. If sufficient confidence has been developed, in some cases the physician may permit the patient to leave the office without having had direct patient-physician contact. In terms of productivity and as a decision point for the physician, this is the most significant deviation away from the traditional system of operation.

At this point, the essential dimensions of the parallel strategy have been implemented and the productivity of the unit is directly dependent upon the extent of patient management delegation and the extent to which verbal consults are required. The physician has two control mechanisms over this strategy: the types of patient visits which are appointed to the physician extender and the verbal consult. Both mechanisms not only provide control over quality of care delivered by the physician extender, but also provide control over the rate at which the physician extender is able to develop additional skills. Theoretically, as the parallel strategy is implemented, the productivity of the unit may double but an eventual increase to about 60 percent of traditional system productivity is seen as a more realistic limit. Finally, if the patient load continues to grow and examining rooms are available, the physician may consider adding and developing other physician extenders and serve increasingly as a consultant to these physician extenders. This would result in evolving to the consultive strategy.

Viewing the traditional, series, parallel and consultive strategies in this evolutionary context suggests that beyond skills and task capabilities of physician extenders, it is the development of mutual trust and confidence between specific persons that determines the strategy employed and consequently the productivity gains that can be achieved. This trust and confidence is expressed operationally at certain decision points for the physician: allowing appointments to be made directly with the physician extender; permitting patients to be cared for in the office without a physician-patient encounter; permitting patients to leave the office after receiving care without the physician having been consulted specifically about their disposition.

Summary

Beyond technical, ethical and legal considerations, the role of a physician extender in a physician's office is obviously up to the physician. However, the potential of physician extenders is to permit the physician to be more productive. Alternative strategies for using physician extenders can be identified which appear to have different potentials for gaining productivity. These strategies differ in certain key dimensions, each of which is related to a critical decision point on the part of the physician. These decisions, viewed in an evolutionary context, rest upon the mutual trust and confidence between physician and physician extender. The results of these decisions dic-

tate not only the productivity of the practice, but the extent to which the physician must devote time or desires to be a manager or consultant for care rather than a direct provider of care.

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Managing Cardiac Tamponade

At Charity Hospital in New Orleans we have a trauma service that I think represents about 60 percent of all our surgical load. It's not unusual to see 10 or 11 instances of tamponade within a given month. When one sees a patient undergoing tamponade, don't try to make the diagnosis on a chest film. Almost invariably, in acute tamponade, you don't get the bottle-sized heart—that's chronic pericardial effusion. These patients often have a small heart. It may be an emergency film and it may not be adequate. You don't always see an elevated central venous pressure, particularly if the tamponade is severe enough so that cardiac output is impinged upon. In fact, the central venous pressure may even be zero at times. A high index of suspicion, really, is about the only thing you have to go on in a penetrating injury (gunshot wound or stab wound) usually in the region of the heart. If there's any question at all, don't hesitate to do a pericardiocentesis.

—THEODORE DRAPANAS, MD, *New Orleans*
Extracted from *Audio-Digest Surgery*, Vol. 22, No. 12, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Boulevard, Suite 700, Los Angeles, CA 90057.

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Physician's Assistants in California

LAURIE S. OSERAN, MS, *San Francisco*

A Socioeconomic Report of the Bureau of Research and Planning
California Medical Association

THERE ARE AT PRESENT more than 50 accredited programs training physician's assistants (PA's) in the United States, and between 1,800 and 2,000 physician's assistants are employed within the health system. Legislation permitting physician's assistants to practice has been enacted in 37 states. Eight educational programs offer such training in California, and so far approximately 100 physician's assistants have been accepted to practice under approved physician supervisors by the Board of Medical Examiners.

California has been in the forefront in the development of the physician's assistant and instrumental in the progress of the midlevel health practitioner concept. AB 2109, the Physician's Assistant Law of 1970, which legally recognized a new category of health manpower in California, established a framework for developing training programs and practice standards and pushed the physician's assistant onto the front line of patient care.

This report deals with the background and development of physician's assistant programs, outlines some of the enabling legislation in California and notes some of the difficulties in assuring that this potential pool of qualified and motivated personnel is employed appropriately to increase the availability of primary health care.

Reprint requests to: Bureau of Research and Planning, California Medical Association, 731 Market Street, San Francisco, CA 94103.

Background

The United States is in a period in which a large proportion of physicians are providing specialized services while patients continue to expect and need individual health care. Magnifying the problem is the situation of manpower maldistribution, which affects remote rural areas most seriously. The unequal distribution of physicians, coupled with the reemergence of demand for general health services, has led to a search for alternative means of providing primary care.

While many imaginative and innovative ideas have been proposed, one of the most promising is the development of a new category of health manpower: the physician's assistant. The idea of a physician's assistant is neither new nor unique to this country. The Chinese barefoot doctor, the Russian feldsher and the African assistant medical officer are all well known in their own environments. Coincidentally, at the time when the need became apparent for a midlevel health practitioner,* approximately 30,000 medical corpsmen returning from Vietnam provided a pool of available, skilled and trained manpower.

Advantages such as the following are immediately apparent:

- Physician's assistants can be trained to handle commonplace illnesses. A physician can

*Midlevel health practitioner is a generic term often used to identify physician's assistants. Within the context of this report this term will be used to refer to the physician's assistant.

delegate responsibilities, while concentrating his own time on complex medical problems requiring his special expertise and attention.

- Utilization of physician's assistants in medical shortage areas can augment access to medical care.
- Employment opportunities are created for persons interested in patient management.
- Training is far less extended and expensive than that required for a physician.

In 1965 Dr. Eugene A. Stead pioneered at Duke University the first physician's assistant program. Focusing on clinical medicine, this two-year program provided corpsmen with additional skills and needed credentials. The Medex Model, designed for military medical personnel, was set up at the University of Washington in 1969 by Dr. Richard Smith. The program combines three months of clinical training with a 12-month preceptorship in a medically underserved area. Both programs have served as models for training PA's.

What Is a Physician's Assistant?

With the development of this new class of health manpower, it became necessary to define a physician's assistant according to appropriate legal statutes, practice environment and tasks and functions.

By statutory requirements a physician's assistant in California must work under the direct supervision of a physician. Tasks undertaken by a physician's assistant are delegated by the supervising physician. Sadler, Sadler and Bliss in *The Physician's Assistant—Today and Tomorrow* assert that by definition the term "physician's assistant" signifies dependence. They state, "The success of the physician's assistant is attributable in large part to his close and dependent relationship with the traditional captain of the health team—the physician."[1]

In a discussion of the physician's assistant, the American Medical Association provides the following definition:

"The assistant to the primary care physician is a person qualified by academic and clinical training to provide patient care services under the supervision of a licensed physician in a wide variety of medical care settings which are involved in the delivery of primary care. The functions of a primary care physician are interdisciplinary in nature involving medicine, pediatrics, obstetrics and psychiatry. . .

"The assistant, therefore, is involved in helping the primary care physician provide a variety of personal health services, including but not limited to:

- receiving patients, obtaining case histories, performing an appropriate physical examination, and presenting meaningful resulting data to the physician;
- performing or assisting in laboratory procedures and related studies in the practice setting;
- giving injections and immunizations;
- suturing and caring for wounds;
- providing patient counseling services; referring patients to other health care resources;
- responding to emergency situations which might arise in the physician's absence within the assistant's range of skills and experience; and
- assisting the employing physician in all settings such as the office, hospitals, extended care facilities, nursing home, and the patient's home.

"The ultimate role of the assistant and his functions vary with his individual capabilities and the specific needs of the employing physician, the practice setting in which he works, and the community in which he lives."[2]

Under California law, the function of a physician's assistant is given binding definition. However, many knowledgeable observers suggest that physician's assistants, as part of an interdisciplinary health team, should have a more flexible definition of role—one allowing for varying situations and based on tasks actually done. Furthermore, increasing specialization within the profession complicates any attempt to define precisely and permanently this midlevel health practitioner.

EXISTING LEGISLATION

The Physician's Assistant Law of 1970

California Assembly Bill 2109, often called landmark legislation in this field, became law on November 23, 1970. Predicated on the existence of shortage and maldistribution of health manpower, AB 2109 legally sanctioned the new classification of physician's assistant. Under this law, the State Board of Medical Examiners was charged with the responsibility of developing educational programs, establishing a system of certification and licensure, and guaranteeing quality health care for Californians. The law has served as a model for similar legislation in other states and for adapting medical practice acts to encourage the use of physician's assistants.

Under its legislative mandate, the Board of Medical Examiners established the Advisory

Committee on Physician's Assistant and Nurse Practitioner Programs. Composed of medical and allied health personnel, the Committee was charged with determining educational and supervision requirements and licensure standards for PA's. Close liaison has been maintained with state agencies and consumer groups to insure that AB 2109 is properly implemented. The Advisory Committee has also been instrumental in fostering legislation, influencing public policy and advocating institutional changes to encourage the use of physician's assistants in California.

While AB 2109 was originally considered innovative and sound, many critics of this statute now contend that its regulations—which explicitly circumscribe and define the tasks physician's assistants can carry out—preclude proper use of their special skills and expertise. In most circumstances the education and training of the PA is far more sophisticated than his actual scope of practice. For example, in an article on licensure for PA's, Blair L. Sadler questions the farsightedness of AB 2109, observing that "The California experience shows the dangers of trying to overregulate a newly emerging health profession at a time when flexibility and innovation are essential."[3]

CURRENT LEGISLATION

A Physician's Assistant Examining Committee

A Physician's Assistant Examining Committee that has the authority to "issue certificates, establish qualifications, standards and guidelines for physician's assistants which are now vested in the Board" was established under recent legislation. Assembly Bill 392, introduced by Assemblyman Gordon Duffy and signed into law on September 9, 1975, became effective January 1, 1976. This bill enables independent approval of a supervising physician and a physician's assistant —which eliminates the traditional, dependent employment relationship between the two. The Examining Committee can adopt regulations concerning the educational qualifications and practice of physician's assistants in California as well as make specific legal determinations on disciplinary matters.

The Examining Committee is charged with developing standards for testing physician's assistants, establishing curriculum and approving training programs. Under this legislation the Board of Medical Examiners can establish guidelines for approval of applications by licensed physicians to supervise physician's assistants and set standards for practice. The composition of the Committee has been changed to include a graduate of an approved physician's assistant training program.

CURRENT LEGISLATION

Assistants to Emergency Care Physician

Signed into law on October 1, 1975, Senate Bill 337 delegates authority to the director of an emergency room in a hospital with an approved training program to grant "interim approval" to emergency care physicians to supervise physician's assistants while awaiting official approval from the Board of Medical Examiners. Predicated on the assumption that there is a shortage of emergency care health personnel, SB 337 allows immediate employment of physician's assistants by emergency care physicians.

The fee requirement for approval of an emergency care physician to supervise a physician's assistant is changed by SB 337. A flat application fee is now required for all supervising physicians employed in the emergency room of a teaching hospital that has an approved training program for physician's assistants. This bill became effective January 1, 1976.

Current Educational Programs

The more than 50 programs training physician's assistants in the United States operate in settings ranging from community hospitals with college affiliation to health science centers. As noted, eight such programs are in California. Three programs (operated by the University of California, Los Angeles/Charles R. Drew Postgraduate Medical School, Foothill College/Stanford University Hospital and the University of Southern California/Los Angeles City College) are engaged in training primary care physician's assistants. Training for emergency care PA's is offered by the University of Southern California/Los Angeles County Medical Center, the University of California, Los Angeles/Charles R. Drew Postgraduate Medical School and Foothill College/San Jose Hospital. A training program for orthopedic PA's is operated by the University of Southern California/Cerritos College. A recent addition is a program of the University of San Diego/University of California, San Diego, Medical School that offers training for the allergy physician's assistant.

Students training to become PA's are generally between four and eight years older than freshman

entering liberal arts colleges. Many have had earlier experience as allied health personnel, for example, as laboratory technicians, respiratory therapists and military corpsmen. With such experience, their professional competency is immediately increased.

The California State Board of Medical Examiners reported in January 1976 that 100 physician's assistants had been approved for practice and nearly all of these are now employed. A total of 135 applications to supervise physician's assistants have been received by the Board from physicians and approximately 100 applications to supervise have been approved.

The average salary range for the physician's assistant in California is estimated by the Board of Medical Examiners at between $822 and $1,200 a month, with some earning as much as $1,500 a month. The salaries of PA's tend to be higher than those of other midlevel health practitioners.

THE CREDENTIALING SYSTEM

Licensure, Certification, Accreditation

The credentialing system for health manpower is generally a three-step process: licensure, certification and accreditation. Licensure for physician's assistants is usually conducted through a designated state agency or commission, and certification of manpower and/or accreditation of education or training programs is often vested in a professional or private organization. Many critics of licensure policies have proposed development of a single health personnel licensure system through a designated state agency which would consolidate existing boards, halt proliferation of licensing agencies and provide uniform standards for regulation. Credentialing requirements determine use and supply of health manpower, geographic distribution and quality of care.

Model for Regulating the Physician's Assistant

Two approaches for regulating physician's assistants have generally been used nationally: amendment of a state medical practice act giving the supervising physician authority to use a PA under his direction or authorization of a state agency (often the State Board of Medical Examiners) to develop rules, requirements and regulations for PA's. In California, the latter approach is used.

Since 1971, the Advisory Committee on Physician's Assistant and Nurse Practitioner Programs has had sole responsibility of regulating PA's in California. The Advisory Committee has been instrumental in developing educational and supervision requirements, delineating performance tasks and setting continuing education requirements for PA's.

In California, educational programs for the training of PA's must be approved by the Board of Medical Examiners. To receive approval for practice in California, a PA must "successfully complete" the Primary Care Physician's Assistant Examination developed jointly by the National Board of Medical Examiners and the American Medical Association in 1972, and administered by the National Board. He must also be a graduate of a program approved by the Board of Medical Examiners. The examination assesses the academic knowledge of the PA and his competency in applying training to a practice situation. The Advisory Committee report asserts that while the "National Board will recommend pass/fail standards, each state regulatory body will have the ultimate responsibility for licensure and certification of the PA."[4] In 1973 the first examination was administered to certify primary care physician's assistants. To date, more than 770 people have passed that examination.

The application process for approval of a physician's assistant and a Supervising Physician (SP), which formerly took a long time, has recently been expedited by changes in administrative procedure. Nevertheless, a PA and SP must be approved by the Board as a double entity; that is, the application of both the physician's assistant and the supervising physician must be jointly approved based on a proposed employment relationship between the two. The physician seeking approval to supervise a PA must provide information to the Board on his educational background, specialty, hospital staff privileges, membership in professional organizations and participation in continuing education programs.[5] He must also provide the Board with a description of the nature and location of his practice. Grounds for denying approval and revoking or suspending the license of a supervising physician include his failure to meet the minimum continuing education requirements satisfactory to the Board.

One clinical residency requirement for students of primary care education programs states that a student can receive full academic credit through equivalency approval, but must also fulfill a minimum of a year in residence in full-time clinical

training with direct patient contact. To encourage interstate reciprocity of health manpower, California and New York require that PA applicants who have received prior approval in another state must provide documentation of their equivalent educational requirements for Board approval.

The process of reimbursement creates another interesting situation—physician's assistants are not allowed to bill separately for their services. Charges for the services of a PA must be included as part of the "global" services provided by a physician.

Supervision requirements for PA's have stirred concern, question and controversy and still represent an unresolved issue. The definition of supervision of a PA, as outlined in Section 1379.22 of the regulations of the California Administrative Code, requires that the supervising physician

> "review separately or together with both the Assistant and the patient the findings of the history, physical examination, and incidental laboratory, radiographic or other diagnostic procedures undertaken by the Assistant before the initiation of any therapeutic procedure."[6]

Consequently the physician must be consulted before even routine medical procedures can be carried out by the PA, a process that is time consuming and logistically impossible in remote rural areas where a physician is not always readily available for immediate consultation.

The definition does specify, however, that the supervising physician is not required to be present when the PA is rendering services in an emergency situation before the physician's arrival or when "attending the chronically ill at home, extended care facility or nursing home merely for the purpose of collecting data for the information and use of the supervising physician."[6]

Section 1379.23 of the regulations, which delineates the tasks that may be performed by an Assistant to the Primary Care Physician, includes an "elastic clause" allowing him to carry out additional tasks contingent upon demonstration to the Board of special skills and competency. This factor, often overlooked, gives a PA some additional freedom.

Some Questions About the Future

Employed properly, physician's assistants can be effective primary care extenders in California. However, the following factors will determine to a great extent the proper use and assimilation of physician's assistants into the state's health manpower pool.

- *Supervision and Distribution*—There continue to be deficiencies in the availability of primary care services in isolated rural areas, as well as in certain urban areas. While use of physician's assistants is a promising way to provide primary care services in medically underserved areas, current supervision requirements for PA's are extremely restrictive and require that a physician be physically present for consultation. In remote areas this is often impossible. It has been suggested that if the current supervision requirements were revised so that a supervisiing physician were accessible through electronic means, this might increase the availability of primary care services by physician's assistants in shortage areas.

- *Cost Effectiveness*—It has not been proven that use of physician's assistants is cost effective in all circumstances. While the time and cost of education of a physician's assistant is considerably less than that required for a physician, reimbursement by third party payers for physician's assistants is sometimes inadequate and often entirely precludes their use. Furthermore, while California law prohibits a physician's assistant from billing separately for his services, debate continues as to whether a physician should reduce fees for services provided by a physician's assistant. If this is not done, cost effectiveness to the patient or the third party may be totally absent. If the PA's charges are lower than those of the physician, however, a two-class medical care system can be created, with the poor receiving one class of care and the affluent another. The Social Security Administration is now conducting a study to determine appropriate methods and levels of reimbursement provided under federal health insurance programs for services by physician's assistants.

- *Legal Concerns*—Those tasks that can be done by a physician's assistant in California are outlined in AB 2109. This law closely defines the supervising physician's liability for medical error. The current professional liability situation and the high cost of malpractice insurance may serve as a deterrent to employment of physician's assistants by physicians. Uniform guidelines for malpractice insurance for physicians who employ physician's assistants have not been set. Provisions for physician's assistants in insurance policies of physicians vary according to company and

may include a percentage add-on rate, a fixed flat fee or no extra charge. The absence of standard policy on this issue has slowed the assimilation of PA's into our health system.

If appropriate responses can be developed to legitimate concerns such as these, significant numbers of physician's assistants may soon move into the roles within the health care system for which the concept was originally designed.

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Abstinence in the Recovery from Alcoholism

In accordance with data currently available, the California Medical Association, along with the National Council on Alcoholism and its medical component, the American Medical Society on Alcoholism, takes the followng position:

Abstinence from alcohol is necessary for recovery from the disease of alcoholism.

Abstinence should not, however, be regarded as the sole criterion for recovery. Other factors by which a person's life are enriched are important, such as improved physical and emotional health, better work performance, more rewarding relationships with the family and society, and increased economic efficiency.

As in many other diseases, relapses may take place but must never be thought to indicate that recovery is beyond reach. Total success is not expected in all cases from the start of treatment. Any improvement is positive and should be recognized and encouraged as a prelude to recovery.

There is a need for responsible research carried out with proper controls as well as the judicious publication of results when pertinent.

However, in the present state of our knowledge, we firmly believe and emphasize that there can be no relaxation from the stated position that no alcoholic may return with safety to any use of alcohol.

Approved by the California Medical Association Committee on Alcoholism and Other Drug Dependence, April 12, 1975; the Executive Committee of the CMA Scientific Board, April 23, 1975, and the CMA Council, May 16, 1975.

in memoriam

Brown, Joseph Mark, Eureka. Died January 6, 1976 in Santa Rosa, aged 72. Graduate of Jefferson Medical School of Thomas Jefferson University, Philadelphia, 1933. Licensed in California in 1935. Dr. Brown was a retired member of the Humboldt-Del Norte County Medical Society.

Daniels, Willie LeBaron, Oakland. Died December 27, 1975, aged 42. Graduate of Howard University College of Medicine, Washington, 1963. Licensed in California in 1967. Dr. Daniels was a member of the Alameda-Contra Costa Medical Association.

Davis, Philip Bruce, Burbank. Died December 12, 1975 in New Mexico in a plane crash, aged 56. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1944. Licensed in California in 1944. MD degree from California College of Medicine, 1962. Dr. Davis was a member of the Los Angeles County Medical Association.

deCarle, Donald Wilson, San Francisco. Died January 2, 1976 in San Francisco of cerebrovascular accident, aged 78. Graduate of the University of Minnesota Medical School, Minneapolis, 1923. Licensed in California in 1932. Dr. deCarle was a member of the San Francisco Medical Society.

Eckhardt, Carl Lambert, Riverside. Died January 3, 1976 in Riverside of injuries received in a November 19 traffic accident in Anaheim, aged 68. Graduate of the University of Minnesota Medical School, Minneapolis, 1936. Licensed in California in 1946. Dr. Eckhard was a member of the Riverside County Medical Association.

Gates, Russell, Santa Barbara. Died December 18, 1975, aged 77. Graduate of the University of Minnesota Medical School, Minneapolis, 1923. Licensed in California in 1935. Dr. Gates was a retired member of the Medical Society of Santa Barbara County.

Goldberg, Robert C., Berkeley. Died December 20, 1975 in Oakland, aged 51. Graduate of Harvard Medical School, Boston, 1955. Licensed in California in 1958. Dr. Goldberg was a member of the Alameda-Contra Costa Medical Association.

Harris, Pauline L., San Marino. Died July 12, 1975, aged 75. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1929. Licensed in California in 1929. MD degree from California College of Medicine, 1962. Dr. Harris was a member of the Los Angeles County Medical Association.

Lorentz, Robert, jr., San Francisco. Died December 13, 1975, aged 87. Graduate of Cooper Medical College, San Francisco, 1912. Licensed in California in 1912. Dr. Lorentz was a retired member of the San Francisco Medical Society.

Martin, George A., Redding. Died December 4, 1975 in Redding, aged 61. Graduate of Northwestern University Medical School, Chicago, 1943. Licensed in California in 1946. Dr. Martin was a member of the Shasta-Trinity County Medical Society.

Miller, James R., Redlands. Died December 23, 1975, aged 43. Graduate of Temple University School of Medicine, Philadelphia, 1957. Licensed in California in 1968. Dr. Miller was a member of the San Bernardino County Medical Society.

Moffat, William M., Santa Barbara. Died January 10, 1976 in Santa Barbara, aged 82. Graduate of Rush Medical College, Chicago, 1924. Licensed in California in 1925. Dr. Moffat was a retired member of the Medical Society of Santa Barbara County.

Moulton, Rowland Richard, San Mateo. Died December 3, 1975 in San Mateo, aged 69. Graduate of the University of California Medical School, Berkeley-San Francisco, 1932. Licensed in California in 1932. Dr. Moulton was a retired member of the San Mateo County Medical Society.

Newman, Donald David, San Gabriel. Died January 11, 1976 in Alhambra of heart disease, aged 54. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1953. Licensed in California in 1954. MD degree from California College of Medicine, 1962. Dr. Newman was a member of the Los Angeles County Medical Association.

Randall, Harriet B., Glendale. Died December 28, 1975 in Glendale of cancer, aged 71. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1929. Licensed in California in 1929. Dr. Randall was an associate member of the Los Angeles County Medical Association.

Shirley, Robert G., Malibu. Died December 23, 1975 in Santa Monica of heart disease, aged 66. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1936. Licensed in California in 1937. Dr. Shirley was a member of the Los Angeles County Medical Association.

Skelly, John Francis, Sacramento. Died January 5, 1976 in Sacramento, aged 67. Graduate of George Washington University School of Medicine, Washington, DC, 1934. Licensed in California in 1934. Dr. Skelly was a retired member of the Santa Clara County Medical Society.

Taylor, Billy Ben, Kelseyville. Died December 23, 1975 in the Canal Zone, aged 51. Graduate of the University of Oklahoma School of Medicine, Oklahoma City, 1952. Licensed in California in 1953. Dr. Taylor was a member of the Alameda-Contra Costa Medical Association.

Waitzfelder, Frederic, Los Angeles. Died December 25, 1975, aged 83. Graduate of Ludwig-Maximilians-Universität Medizinische Fakultät, München, 1917. Licensed in California in 1926. Dr. Waitzfelder was a member of the Los Angeles County Medical Association.

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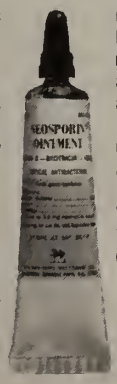

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FUTURE MEDICAL/DENTAL SITE located on Dyer off Alvarado Blvd. in Union City, California. Population 32,000, with no medical assistance. For information, contact: Darlene Souza, (415) 483-8300.

HOUSE FOR SALE

ELLSWORTH, MAINE: Area in need of medical services. Turn of century 17-room show place. Gourmet kitchen. 8 beds, 3½ baths, conservatory. Near salt water. 5 hospitals in area. $125,000. H. Dickinson, 12 W. Maple, Ellsworth, Maine 04605; (207) 667-2277.

OFFICES FOR RENT OR LEASE

FOR RENT: The newest and largest professional building in the South San Diego community of Imperial Beach, suites available can be customized to suit tenant. This is excellent opportunity for pediatrics, gynecology, dermatology, ophthalmology, general surgery, general practice, internal medicine and psychiatry. Photos and particulars available upon request from John E. Geis, DDS, 1340 Coronado Ave., Suite 201, Imperial Beach, CA 92032; office (714) 424-3931.

MEDICAL SUITE AVAILABLE in the Foothill Medical Building, 21297 Foothill Blvd., Hayward, CA 94541. It consists of 850 sq. ft., 3 treatment rooms, waiting room, nurses station and private doctor's office. The building has an x-ray and medical laboratory, and a pharmacy. It is currently occupied by Family Practice Physicians predominantly. For information call (415) 582-6942.

LARGE OFFICE for group. 2,400 sq. ft., x-ray and laboratory. Close to hospital, well designed. B. Berger, MD, Pinole, CA; (415) 758-2511.

OFFICE FOR LEASE, TUCSON, ARIZONA—825 sq. ft. next to St. Mary's Hospital. Furnished or unfurnished. 1701 W. St. Mary's Rd., No. 171, Tucson, Arizona 85705; (602) 623-5479.

MODERN MEDICAL OFFICE—Over 1,500 sq. ft. —off street parking—x-ray and laboratory in building—42 cents per sq. ft.—all utilities paid —write or call E. P. Doemeny, MD, 4260 54th Street, San Diego, 92115; (714) 286-3222.

PROFESSIONAL MEDICAL BILLING

MEDI-CAL/MEDICARE BILLING AND ACCOUNTING for private physicians. Can work as regular consultant or professional biller. $5 per hour or arranged percentage. Call evenings. Terry L. Parkinson, 87 Noe Street, San Francisco, CA 94114; (415) 431-2150.

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INFORMATION

(415) 777-2000

FOR LEASE: Large office ideal for small group located in Lawndale, California. Near Hawthorne Community Hospital and Gardena Memorial. Contact **Allen Hooper, MD, 1200 N. State St. P.O. Box 313, Los Angeles, CA 90033; Phone (213) 226-6675.**

The Equitable Life Assurance Society will establish a Regional Office in Fresno, California and has openings for two physicians in life insurance medicine. California license is necessary. Preference will be given to qualified physicians in internal medicine with at least five years clinical experience. Previous experience in insurance medicine desirable but not essential. Compensation will be competitive with excellent fringe benefits including malpractice coverage. We are an equal opportunity employer.

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CONTINUING MEDICAL EDUCATION

California, Hawaii • Oregon • Washington, Montana, Alaska, Idaho

CALIFORNIA and HAWAII

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: For a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education, please write to the above address.

ALCOHOLISM AND DRUG ABUSE

April 3—**Poly Drug Abuse.** USC. Saturday.

May 21-23—**Alcoholism and Drug Abuse.** UCSF. Friday-Sunday.

May 27-29—**National Conference on Radiation Oncology.** American Cancer Society at Hilton Hotel, San Francisco. Thursday-Saturday. Contact: S. L. Arje, MD, ACS, 777 3rd Ave., New York 10017.

CANCER

March 26—**Colo-Rectal Carcinoma.** California Hospital Medical Center, Los Angeles. Friday. 10 hrs. $15. Contact: Kenneth L. Senter, MD, Dir., Med. Ed., CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411.

April 3—**Oncology Update 1976.** Alta Bates Hospital, Berkeley. Saturday. 8 hrs. $20. Contact: Norman Cohen, MD or Harry Newman, MD, Alta Bates Hospital, No. 1 Colby Plaza, Berkeley 94705. (415) 845-7110.

MEDICINE

March 20—**Echocardiography Workshop.** PMC at Miyako Hotel, San Francisco. Saturday.

March 22-April 2—**Intensive Review of Internal Medicine—24th Annual.** USC. Two weeks.

March 24-26—**Hepato-Biliary Disease.** PMC at Mark Hopkins Hotel, San Francisco. Wednesday-Friday.

March 26-27—**Pulmonary Artery Catheterization.** PMC. Friday-Saturday.

March 26-27—**New Perspectives in Exercise Stress Testing.** American College of Cardiology; Memorial Hospital Medical Center, Long Beach; UCI at Center for Health Education, Memorial Hospital, Long Beach. Friday-Saturday. Contact: ACC, 9650 Rockville Pike, Bethesda, MD 20014.

March 30-April 2—**Consultant's Course in Dermatology.** UCSF. Tuesday-Friday.

April 1-2—**Current Problems in Intensive Care: Pulmonary Edema.** UCSF at St. Francis Hotel, San Francisco. Thursday-Friday.

April 1-2—**Core Curriculum: Cardiovascular Physiology: Clinical Implications of Newer Concepts and Measurements.** American College of Cardiology at Cedars-Sinai Medical Center, Los Angeles. Thursday-Friday. Contact: ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

April 1-3—**Advances in Cardiology.** Foundation for Cardiovascular Research and Hospital of the Good Samaritan at Balboa Bay Club, Newport Beach. Thursday-Saturday. Contact: Foundation for Cardiovascular Research, 39 Congress St., Pasadena 91105.

April 2-3—**Recent Advances in Endocrinology.** USC at Erawan Gardens, Palm Springs. Friday-Saturday.

April 3—**Gastroenterology Symposium.** Central Calif. Committee for Gastroenterology at Fresno Community Hospital. Saturday. $25. Contact: Mr. Remi Barron, Central San Joaquin Valley Area Health Education Center, 5110 E. Clinton Way, Suite 115, Fresno 93727. (209) 252-2851.

April 5-14—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe. 10 days. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

April 6-July 13—**Intensive Review of Recent Advances in Internal Medicine.** UCLA. Tuesdays, 7-10 p.m. 57 hrs. $135.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

THE UNIVERSITY OF SOUTHERN CALIFORNIA SCHOOL OF MEDICINE

presents **A POSTGRADUATE COURSE**

MANIPULATIVE MEDICINE AND RELATED TECHNIQUES IN THE TREATMENT OF MUSCULO-SKELETAL PAIN

THURSDAY, FRIDAY AND SATURDAY • APRIL 29, 30, MAY 1, 1976

This course is designed to present to the practicing physician, by appropriate lecture and workshops, the concept and role of manipulation and related techniques in the treatment of painful musculo-skeletal disorders.

The emphasis will be placed on the practical aspects of the application of these techniques to specific problems encountered in everyday practice.

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Manipulative Medicine and Related Techniques in the Treatment of Musculo-Skeletal Pain
April 29, 30 and May 1, 1976
Course No. 790

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Registration Fee: $200 (includes meals and parking) **Resident's Fee: $150**

Make checks payable to University of Southern California and send to Associate Dean, USC School of Medicine, Postgraduate Division, 2025 Zonal Avenue, Los Angeles, CA 90033. Phone: (213) 226-2051.

April 11-16—**American Association of Immunologists.** Royal Hotel, Anaheim. Sunday-Friday. Contact: H. Metzger, MD, Sec.-Treas., AAI, 9650 Rockville Pike, Bethesda, Md. 20014.

April 26-30—**Advances in Internal Medicine.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday.

April 29—**Annual Physicians' Cardiovascular Symposium—Cardiology 1976.** American Heart Association, Central Valley Chapter, at Hilton Hotel, Fresno. Thursday. $35. Contact: AHA, Central Valley Chapter, 3835 N. West Ave., Fresno 93705. (209) 224-8215.

April 30—**Flexible Bronchofibroscopy II.** PMC. Friday.

May 6-8—**Arrhythmias: Basic and Clinical Aspects.** PMC at Golden Gateway Holiday Inn, San Francisco. Thursday-Saturday.

May 7-8—**Coagulation Update 1976.** UCSF. Friday-Saturday.

May 14—**American Heart Association, California Affiliate—Scientific Sessions for Physicians.** Hotel Del Coronado, Coronado. Friday. 6½ hrs. $25. Contact: Marilyn Probst, Admin. Asst., AHA, Calif. Affiliate, 1370 Mission St., San Francisco. (415) 626-0123.

May 18—**Seminars in Nephrology.** USC. Tuesday.

May 21—**Diagnosis and Treatment of Hypertension.** PMC. Friday.

OBSTETRICS AND GYNECOLOGY

April 2-3—**Obstetrics and Gynecology: Workshop in Intrapartum Fetal Monitoring.** UCSF. Friday-Saturday.

May 15-16—**Gyn-Urology.** USC at Biltmore Hotel, Santa Barbara. Saturday-Sunday.

PEDIATRICS

March 19-21—**Combined Southern California Pediatric Postgraduate Meeting: Clinical Pediatrics.** Calif. Chapter 2, District IX, American Academy of Pediatrics, at Riviera Hotel, Palm Springs. Friday-Sunday. Contact: Eve Black, Exec. Sec., P.O. Box 2134, Inglewood 90305.

March 20—**Pediatric Subspecialty Problems in Office Practice.** Mt. Zion Hospital & Medical Center, San Francisco. Saturday. $40. 6 hrs. Contact: Continuing Education, Mt. Zion Hospital & Medical Center, P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2401.

March 26-27—**Pediatric Topics 1976: Neonatology and Pediatric Cardiology.** UCD and Sacramento Pediatric Society at Mansion Inn, Sacramento. Friday-Saturday. Contact: UCD.

April 23-24—**Pediatric Ophthalmology.** See Surgery, April 23-24.

April 24-May 1—**Pediatric Review.** USC at Maui Surf, Hawaii. One week.

May 3-7—**Pediatric Review—6th Annual.** USC. Monday-Friday.

May 8-9—**Learning Disabilities in Children.** UCLA. Saturday-Sunday.

May 13-15—**Annual Pediatric Course.** UCSF. Thursday-Saturday.

May 21-23—**American Academy of Pediatrics, California Chapter I, District IX.** Ahwahnee Hotel, Yosemite. Friday-Sunday. Contact: Melvin H. Schwartz, MD, 2219 Santa Clara Ave., Alameda 94501.

May 23-26—**Recent Advances in Pediatric Neurology.** UCLA at Ahwahnee Hotel, Yosemite. Sunday-Wednesday.

PSYCHIATRY

March 18—**The Compromised Psychophysiologic State or "Why Can't You Make Me Well?"** See Of Interest To All, March 18.

April 2-4—**The Interface of Medical Practice and Psychiatry: A Symposium on Psychosomatics and Psychiatry in Medicine.** Children's Hospital, Marshal Hale Memorial Hospital, San Francisco Psychoanalytic Institute at Children's Hospital, San Francisco. Friday-Sunday. 12 hrs. $100. Contact: Office of Medical Education, Children's Hospital, 3700 California St., P.O. Box 3805, San Francisco 94119. (415) 387-8700, ext. 711.

April 11-15—**Psychiatric Update—3rd Annual Seminar.** UCLA at Riviera Hotel, Palm Springs. Sunday-Thursday.

May 8-9—**Learning Disabilities in Children.** See Pediatrics, May 8-9.

May 16-19—**Biofeedback—3rd Annual Program.** UCLA at Ahwahnee Hotel, Yosemite. Sunday-Wednesday.

RADIOLOGY AND PATHOLOGY

March 15-19—**Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday.

March 20-21—**Ultra Sound, A Practical Course.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

March 21-25—**Cardiac Radiology Refresher Course.** North American Society for Cardiac Radiology at Sir Francis Drake Hotel, San Francisco. Sunday-Thursday. Contact: Erik Carlsson, MD, Dept. of Radiology, UCSF.

April 11-16—**American Society for Experimental Pathology.** Anaheim. Sunday-Friday. Contact: Am. Soc. for Experimental Pathology, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-7130.

May 5-8—**Nuclear Medicine—6th Annual Spring Symposium.** Sierra Valley Nuclear Medicine Assn.; No. Calif. Chapter, Society of Nuclear Medicine, at Convention Center, Lake Tahoe. Wednesday-Saturday. Contact: Darleen Nelson, Nuclear Medicine Dept., Mercy San Juan Hospital, 6501 Coyle Ave., Carmichael 95608.

SURGERY AND ANESTHESIOLOGY

March 17-21—**Symposium on Vascular Surgery—4th Annual.** UCLA at Canyon Hotel, Palm Springs. Wednesday-Sunday.

March 18-19—**Diseases of the Urinary Tract—4th Annual Symposium.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday.

March 18-20—**7th Annual Ophthalmological Conference: Clinical-Pathological Review of Ocular Diseases.** St. Mary's Hospital and Medical Center at Hyatt on Union Square, San Francisco. Thursday-Saturday. 20 hrs. $200 advanced registration; $215 at door (includes lunch and cocktail party). Contact: Doctors Sarrail and Silvestri, Co-Chairpersons, 450 Sutter St., San Francisco 94108. (415) 397-1500.

March 22-26—**Anesthesiology—1976.** Anesthesiology Education Foundation and Calif. Society of Anesthesiologists at Mammoth Lakes. Monday-Friday. Contact: Ronald L. Katz, MD, Dept. of Anesthesiology, UCLA.

March 22-26—**Trauma and Surgical Emergencies.** STAN. Monday-Friday.

March 27-30—**Jaws: Reconstructive Surgery of Developmental and Acquired Deformities.** UCLA. Saturday-Tuesday.

April 2—**Corneal Surgery Workshop.** Jules Stein Eye Institute, Los Angeles. Friday. Contact: Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles.

April 7-10—**California Thoracic Society—Annual Scientific Sessions.** Rickey's Hyatt House, Palo Alto. Wednesday-Saturday. Contact: Ms. Elma Plappert, Exec. Sec., CTS, 424 Pendleton Way, Oakland 94621. (415) 638-5864.

April 8-9—**Ophthalmic Skills.** PMC. Thursday-Friday.

April 8-9—**Office Orthopedics.** USC. Thursday-Friday.

April 9-10—**Phacoemulsification Conference.** St. Mary's Hospital and Medical Center, San Francisco. Friday-Saturday. Contact: J. Albert Sarrai, MD, 450 Sutter St., San Francisco. (415) 397-1500.

April 22-23—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

April 22-24—**General Surgery—Annual Course.** UCSF at Hilton Hotel, San Francisco. Thursday-Saturday.

April 23-24—**Pediatric Ophthalmology—A Current Review—7th Annual Jules Stein Lecture and Postgraduate Seminar.** Jules Stein Eye Institute at Beverly Hilton Hotel, Los Angeles. Friday-Saturday. Contact: Jules Stein Eye Institute, UCLA.

April 23-25—**American Association for Thoracic Surgery.** Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Mr. W. T. Maloney, Exec. Sec., 6 Beacon St., Suite 620, Boston, Mass. 02108. (617) 227-0760.

May 1-8—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

May 4-7—**Samuel Higby Camp—Orthopedic Surgery.** UCSF. Tuesday-Friday.

May 15-16—**Gynecology-Urology.** See Obstetrics and Gynecology, May 15-16.

May 16-28—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. 100 hrs. $1,200 for otolaryngologists; $900 for residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

May 20-21—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

May 20-22—**Neurosurgery—6th Annual Postgraduate Course.** UCSF at St. Francis Hotel, San Francisco. Thursday-Saturday.

May 23-26—**Recent Advances in Pediatric Neurology.** See Pediatrics, May 23-26.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

March 18—**The Compromised Psychophysiologic State or "Why Can't You Make Me Well?"** Eden Hospital at Willow Park Country Club, Castro Valley. Thursday. 7 hrs. $35. Contact: Ms. Eleanor Sample, Eden Hospital, 20103 Lake Chabot Rd., Castro Valley. (415) 537-1234, ext. 211.

March 19—**Office Management of Parkinsonism.** PMC at Miyako Hotel, San Francisco. Friday.

March 21-23—**Sports Injury Clinic.** CMA, Medical Education Foundation of Santa Barbara County and UCLA at Lakeland Village, Lake Tahoe. Sunday-Tuesday. Contact: Richard Manley, CMA.

March 22-26—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday.

March 28-30—**Western Gerontological Society—22nd Annual Meeting.** Town and Country Hotel, San Diego. Sunday-Tuesday. Contact: WGS, 1095 Market St., Room 714, San Francisco 94103. (415) 621-7244.

March 29-April 2—**Basic and Applied Pharmacology.** STAN. Monday-Friday.

April 1-2—**Current Problems in Intensive Care: Pulmonary Edema.** See Medicine, April 1-2.

April 1-4—**Problems of Post-Op Care and Maintenance.** St. Joseph's Hospital, Stockton. Thursday-Sunday. Contact: Sister Mary Gabriel, O.P., St. Joseph's Hospital, 1800 N. California St., Stockton 95204.

April 2-4—**The Interface of Medical Practice and Psychiatry: A Symposium on Psychosomatics and Psychiatry in Medicine.** See Psychiatry, April 2-4.

April 8-10—**Otolaryngology for the GP.** UCSF. Thursday-Saturday.

April 23-24—**West Coast Counties Postgraduate Institute.** CMA at Quail Lodge, Carmel Valley. 14 hrs. $60 for CMA members; $90, non-members. Friday-Saturday. Contact: Richard Manley, CMA.

April 24—**5th Annual Symposium—Fluid and Electrolytes—Management in Clinical Practice.** South Coast Community Hospital, South Laguna. Saturday. 8 hrs. $25. Contact: Eugene B. Levin, MD, Dir. of Med. Ed., SCCH, 31872 Coast Highway, South Laguna 92677. (714) 499-1311, ext. 136-137.

April 26-May 1—**Emergency Medicine.** USC at Kauai Surf, Kauai, Hawaii. Monday-Saturday.

April 26-May 1—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Saturday.

April 29-May 1—**Psychosocial Care of Dying Patient—Doctor:Patient Relationship.** UCSF at St. Francis Hotel, San Francisco. Thursday-Saturday.

April 29-May 2—**Medicine and Related Techniques in the Treatment of Musculoskeletal Pain.** USC. Thursday-Sunday.

May 10-15—**Diving Medicine.** UCSF at VA Hospital, Fresno. Monday-Saturday.

May 10-21—**Family Practice—Intensive Review.** USC. Two weeks.

May 14-15—**San Joaquin Valley Counties Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Friday-Saturday. $60 for CMA members; $90, non-members. Contact: Richard Manley, CMA.

May 15—**Clinical Pharmacology Conference.** Stanford Division of Clinical Pharmacology and Palo Alto Medical Research Foundation at Stanford. Saturday. Contact: STAN.

May 17-21—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

May 21—**Diagnosis and Treatment of Hypertension.** See Medicine, May 21.

May 29-30—**Opportunistic Fungus Diseases.** UCSF. Saturday-Sunday.

Audio-Digest Foundation. A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: Family Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $90 per year. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90057. (213) 483-3451.

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Providence Medical Center, 700 NE 47th Avenue, Portland 97213. Contact: Dave Gilbert, MD, Providence Medical Center:

Every Wednesday, 8:00 a.m. to 9:00 a.m.—**Spring Medical Grand Rounds.**

University of Oregon Medical School, Family Practice Center, 3181 S.W. Sam Jackson Park Road, Portland 97201:

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School.

FAMILY PRACTICE

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Family Practice Center, University of Oregon Medical School, Portland. Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

INTERNAL MEDICINE

May 20-22—**Oregon Society of Internal Medicine Annual Meeting.** Sunriver Lodge, Sunriver, Oregon. Contact: Donald R. Olson, MD, Oregon Society of Internal Medicine, 2164 S.W. Park Place, Portland 97205.

PHYSICAL MEDICINE AND REHABILITATION

April 30-May 1—**Northwest Association of Physical Medicine and Rehabilitation Annual Meeting.** Jantzen Beach Thunder-

ADVANCES IN INTERNAL MEDICINE

April 26-30, 1976

FAIRMONT HOTEL
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This program is presented by the Department of Medicine, University of California School of Medicine in cooperation with Extended Programs in Medical Education, University of California School of Medicine, San Francisco, California

This course is designed to provide a broad review in internal medicine with particular emphasis on areas with recent advances in knowledge. The course will be suitable for either the practicing internists who wish a general update in knowledge or candidates for certification by the American Board of Internal Medicine. This program is approved for 40 hours of Category I credit towards the certificate in Continuing Education for the American Medical Association and the California Medical Association.

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CARDIOLOGY ..... ELLIOT RAPAPORT, MD
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PULMONARY ..... WARREN M. GOLD, MD
METABOLISM ..... MARVIN SIPERSTEIN, MD
RENAL ..... FLOYD C. RECTOR, MD
ENDOCRINOLOGY ..... PETER H. FORSHAM, MD
RHEUMATOLOGY ..... NORMAN TALAL, MD

REGISTRATION FEE: $250; $150 for Interns. Residents and members of the Armed Forces will be admitted with letter of verification.

CHECKS should be made payable to: Regents—U.C.

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Extended Programs in Medical Education
Room 569-U
University of California
San Francisco, California 94143

- **FOR REGISTRATION INFORMATION CALL (415) 666-2483 or 666-2894**
- **FOR PROGRAM INFORMATION CALL (415) 666-4251**

bird, Portland. Contact: John E. Stanwood, MD, Emanuel Hospital, 2801 N. Gantenbein, Emanuel East, Room 370, Portland 97227.

SURGERY

April 2-3—**American College of Foot Surgeons, Western Division.** Portland Hilton Hotel, Portland. Contact: Robert L. Rutherford, D.P.M., 400 - 40th Street, Oakland, California 94609

September 6-7—**Western Orthopedic Society Annual Meeting.** Sunriver Lodge, Bend. Contact: Stanley E. Donahoo, MD, 1819 West Harvard Blvd., Roseburg 97470.

OF INTEREST TO ALL PHYSICIANS

March 22—**Bilderbach Lectures.** University of Oregon Health Sciences Center Auditorium. Contact: M. Roberts Grover, Jr., MD, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

March 30-31—**The Elderly and Their Health Care.** Good Samaritan Hospital, Portland. Contact: S. Spence Meighan, MD, Good Samaritan Hospital and Medical Center, 1015 N.W. 22nd, Portland 97210.

WASHINGTON, MONTANA, ALASKA and IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

March 15-19—**Emergency Medicine Institute.** Monday-Friday. Univ. of Wash. Sch. of Med., Seattle. Limited to 16. 38 hrs. $275. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 18-19—**American Society of Clinical Pharmacology and Therapeutics.** Thursday-Friday. Washington Plaza Hotel, Seattle. Contact: E. H. Funk, MD, 1718 Gallagher Rd., Norristown, PA 19401. (215) 277-3831.

March 18-19—**Evaluation and Management of Behavior Problems in the Elderly.** Thursday-Friday. Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 22-26—**Advances in Family Practice.** Monday-Friday. Child Development and Mental Retardation Center, Univ. of Wash., Seattle. Limited to 90. Approximately 35 hrs. $125. Contact Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 25-26—**Immediate Care of the Sick and Injured.** Thursday-Friday. Univ. of Wash. Sch. of Med. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 1-2—**Medical-Dental Management of Oro-facial Pain.** Thursday-Friday. University Tower Hotel, Seattle. Limited to 60. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 1-2—**Clinical Pharmacology for the Practicing Physician.** Thursday-Friday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

April 9—**Gastroenterology for Non-Gastroenterologists.** Friday. Seattle. Limited to 150. Location, hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 12-16—**Emergency Medicine Institute.** Monday-Friday. Univ. of Wash. Sch. of Med., Seattle. Limited to 16. 38 hrs. $275. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 24—**Current Concepts in Nutrition.** Saturday. University Tower Hotel, Seattle. Hours and fees to be determined. Contact Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 22-23—**Respiratory Care Conference.** Thursday-Friday. Olympic Hotel, Seattle. Hours and fees to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 30—**Medicine and Law.** Friday. Seattle. Location, hours and fees to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195 (206) 543-1050.

May 1—**Current Concepts in Nutrition.** Saturday. Spokane. Location, hours and fees to be determined. Contact Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 6-7—**Surgical Therapeutics.** Thursday-Friday. Washington Plaza Hotel, Seattle. Limited to 200. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 7-8—**Regional Block Anesthesia.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

May 9-10—**Postgraduate Conference for Physicians.** Sunday-Monday. Billings, Montana. Contact: John P. Connor, Exec. Dir., Montana State Heart Assoc., 510 First Ave. N., Great Falls 59401. (406) 452-2362.

May 12-14—**Advances in Internal Medicine.** Wednesday-Friday. Olympic Hotel, Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 14-23—**Tax, Estate and Financial Planning.** Friday-Monday. Aboard the SS Rotterdam; 7-day cruise to Nassau and Bermuda. 25 hrs. $200. Contact: Richard L. Reimer, Asst. Dir. CME, T87 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 16-20—**Pacific Coast Oto-Opnthalmological Society.** Sunday-Wednesday. Washington Plaza Hotel, Seattle. Contact: M. F. W. Smith, MD, Ear Medical Clinic of Santa Clara Valley, 2120 Forest Ave., Suite 2, San Jose, CA 95128.

May 20-21—**Pediatric Care for General Practitioners.** Thursday-Friday. Children's Orthopaedic Hospital and Medical Center, Seattle. 12 hrs. $45. Contact: William O. Robertson, MD, Dir. Med. Ed., Children's Orthopaedic Hospital and Medical Center, 4800 Sand Point Way NE, Seattle 98105. (206) 634-5072.

May 21-22—**Sports Medicine—1976.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

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May 24-28—**Treating the Untreatable—Univ. of Washington School of Medicine's Montana Circuit Course.** Great Falls, 24th; Billings, 25th; Bozeman, 26th; Missoula, 27th; Whitefish/Kalispell, 28th. 4 hrs. Physicians, $25; others, $10. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

June 10-11—**Hypertension: Etiology and Factors in Choice of Drugs.** Thursday-Friday. Virginia Mason Medical Center Auditorium, Seattle. 12 hrs. $75. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

June 14-17—**Disorders of Red Cell Proliferation.** (ACP). Sunday-Thursday. Rosario Resort, Orcas Island, WA. Hours to be determined. ASH, ACP members, fellows, residents, $140; non-members, $195; associates, $70. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

June 25—**Bicentennial History of Medicine in the United States.** Friday. Kane Hall, Univ. of Wash., Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

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□ Found useful in the management of vertigo* associated with diseases affecting the vestibular system.
□ Can relieve nausea and vomiting often associated with vertigo.*
□ Usual adult dosage for Antivert/25 for vertigo:* one tablet t.i.d.
□ Also available as Antivert (meclizine HCl) 12.5 mg. scored tablets, for dosage convenience and flexibility.
□ Antivert/25 (meclizine HCl) 25 mg. *Chewable* Tablets for nausea, vomiting and dizziness associated with motion sickness.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

*INDICATIONS. Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Effective: Management of nausea and vomiting and dizziness associated with motion sickness.

Possibly Effective: Management of vertigo associated with diseases affecting the vestibular system.

Final classification of the less than effective indications requires further investigation.

CONTRAINDICATIONS. Administration of Antivert (meclizine HCl) during pregnancy or to women who may become pregnant is contraindicated in view of the teratogenic effect of the drug in rats.

The administration of meclizine to pregnant rats during the 12-15 day of gestation has produced cleft palate in the offspring. Limited studies using doses of over 100 mg./kg./day in rabbits and 10 mg./kg./day in pigs and monkeys did not show cleft palate. Congeners of meclizine have caused cleft palate in species other than the rat.

Meclizine HCl is contraindicated in individuals who have shown a previous hypersensitivity to it.

WARNINGS. Since drowsiness may, on occasion, occur with use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery.

Usage in Children. Clinical studies establishing safety and effectiveness in children have not been done; therefore, usage is not recommended in the pediatric age group.

Usage in Pregnancy: See "Contraindications."

ADVERSE REACTIONS. Drowsiness, dry mouth and, on rare occasions, blurred vision have been reported.

More detailed professional information available on request.

ROERIG Pfizer
A division of Pfizer Pharmaceuticals
New York, New York 10017

Antivert®/25
(meclizine HCl) 25 mg. Tablets
for vertigo*

THE WESTERN Journal of Medicine

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Effectiveness across the spectrum of most common forms of insomnia

Awake too long, awake too often, awake too early...

These are the most common forms of insomnia, and may occur singly or in any combination. The night of troubled sleep depicted here comprises all three types. As the night progresses from left to right, each sleep stage is identifiable by its own shade of gray. Blue represents "Awake."

As you can see, this hypothetical "patient" takes well over an hour to fall asleep, awakens several times during the middle of the night and awakens too early in the morning.

Sleep Stages

- Awake
- REM
- Stage 1
- Stage 2
- Stage 3
- Stage 4

Awake too long

Awake too often during the night

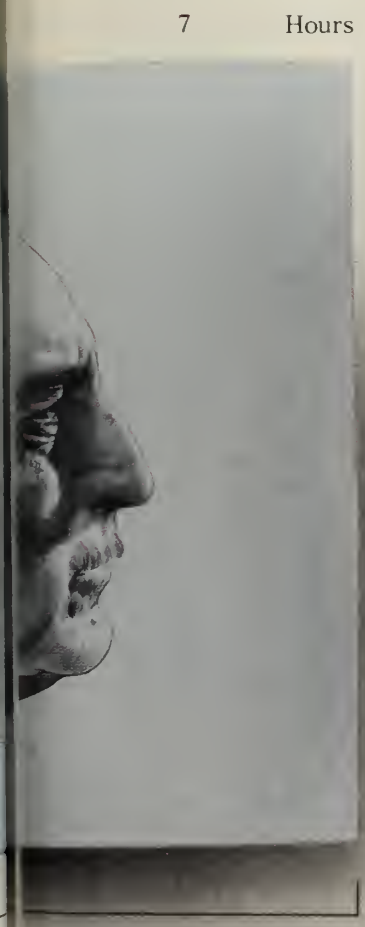
The insomnias most often occurring in young and older adults

For patients with trouble falling asleep (common in young adult insomnia patients), Dalmane (flurazepam HCl) 30 mg provides sleep within 17 minutes, on average. For those with trouble staying asleep or sleeping long enough (common in those over 50), Dalmane offers increased total sleep time with fewer nocturnal awakenings. These clinical results were demonstrated in studies conducted in four geographically separated sleep research laboratories.[1-4]

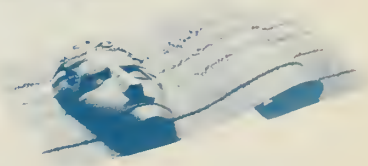
The relative safety of Dalmane (flurazepam HCl) is well documented

Dalmane (flurazepam HCl) is relatively safe and well tolerated; morning "hang-over" has been infrequent. The usual adult dosage is 30 mg; in elderly or debilitated patients, limit initial dosage to 15 mg to preclude over-sedation, dizziness or ataxia. Caution patients about possible combined effects with alcohol and other CNS depressants.

Broad-spectrum medication for the most common forms of insomnia



Awake too early



Dalmane®
(flurazepam HCl)

One 30-mg capsule *h.s.*— usual adult dosage
(15 mg may suffice in some patients).
One 15-mg capsule *h.s.*— initial dosage for elderly or debilitated patients.

- induces sleep rapidly
- reduces nighttime awakenings
- lengthens total sleep time

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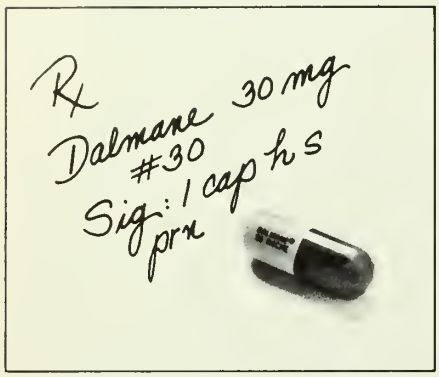
Please see following page for a summary of complete product information.

Broad-spectrum medication for the most common forms of insomnia

Dalmane®
(flurazepam HCl) ℂIV



Objectively proved in the sleep research laboratory, Dalmane

- □ induces sleep within 17 minutes, on average
- □ reduces nighttime awakenings
- □ provides 7 to 8 hours sleep, on average, without repeating dosage

Before prescribing Dalmane (flurazepam HCl), please consult complete product information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

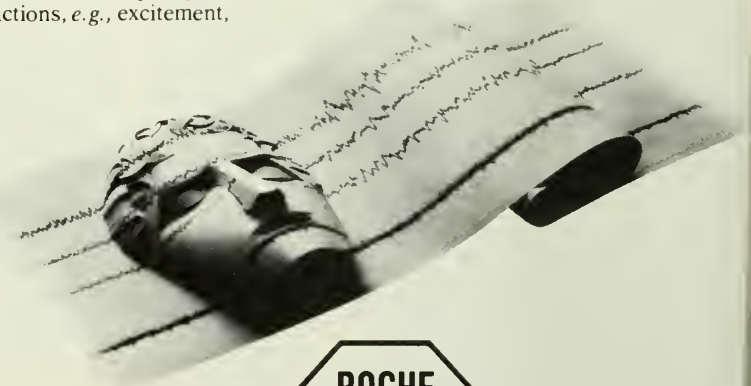
REFERENCES:

1. Karacan I, Williams RL, Smith JR: The sleep laboratory in the investigation of sleep and sleep disturbances. Scientific exhibit at the 124th annual meeting of the American Psychiatric Association, Washington DC, May 3-7, 1971

2. Frost JD Jr: A system for automatically analyzing sleep. Scientific exhibit at the 24th Clinical Convention of the American Medical Association, Boston, Nov 29-Dec 2, 1970; and at the 42nd annual scientific meeting of the Aerospace Medical Association, Houston, Apr 26-29, 1971

3. Vogel GW: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ

4. Dement WC: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ



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FOR LONG-TERM CONTROL OF HYPERTENSION*

Serum K^+ and BUN should be checked periodically. (See Warnings Section.)

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

* **Warning**
This fixed combination drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

***Indications:** *Edema:* That associated with congestive heart failure, cirrhosis of the liver, the nephrotic syndrome; steroid-induced and idiopathic edema; edema resistant to other diuretic therapy. *Mild to moderate hypertension:* Usefulness of the triamterene component is limited to its potassium-sparing effect.

Contraindications: Pre-existing elevated serum potassium. Hypersensitivity to either component. Continued use in progressive renal or hepatic dysfunction or developing hyperkalemia.

Warnings: **Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired.** Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, **check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently**—both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

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(Continued on Page 18)

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MOCHA MIX DATA SHEET

Portion Size 1 Fluid Ounce (2 Tbs.)

Servings per container	16
Calories	40
Protein	0 grams
Carbohydrate	3 grams
Fat	3 grams
Percent of Calories from Fat	73%
Polyunsaturated Fat	1 gram
Saturated Fat	0 grams
Cholesterol	0

(Percentage of U.S. Recommended Daily Allowances (U.S., RDA)*

*Contains less than 2% of the U.S. RDA of Protein, Vitamin A, Vitamin C, Thiamine, Riboflavin, Niacin, Calcium, Iron.

In addition to the pint and quart size found in the dairy case of most grocery stores, Mocha Mix is available in 4 ounce and ½ oz. portion packs for hospitals and institutions.

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Mocha Mix Dept. Presto Food Products, Inc.
P.O. Box No. 21908, Los Angeles, Calif. 90021

mocha mix® ...the non-dairy creamer that's lowest in saturated fat.

In two separate multicenter studies* of patients with chronic or frequently recurrent urinary tract infections

10 days of Bactrim™ therapy produced better results in maintaining clear cultures than:

- 10 days of ampicillin therapy
- 28 days of cephalexin therapy

*Protocols identical except for drug administered and duration of therapy. Protocol details on last page of this advertisement.

Please see summary of product information on last page of this advertisement.

ROCHE

Roche
Research
U.T.I. Study
No. 2

ne month after therapy ceased, a higher percentage f Bactrim-treated patients maintained clear cultures*.

	No. of patients	Therapy	% of clear cultures*
tudy No. 1	80	10-day Bactrim	71.3%
	76	10-day ampicillin	56.6%
tudy No. 2	60	28-day cephalexin	56.7%

ion for clear culture: 1000 or fewer organisms/ml of urine.

month after therapy: 10 days of Bactrim maintained cultures for one month in a larger percentage of nts than either of the other agents. The maintenance ar cultures for one month after therapy has ended particular importance for patients whose problems hronic or recur frequently, for it is during this period elapse or reinfection often occurs.

diately after therapy: Here again, Bactrim results superior. At the end of therapy, 90.4% of 83 patients days of Bactrim had clear cultures, compared with 81.7% of 82 patients on 10 days of ampicillin and 86.6% of 82 patients on 28 days of cephalexin.

Adverse reactions: Side effects in these studies were relatively mild (*e.g.*, nausea, vomiting, rash), but more serious adverse effects can occur with the agents studied. For a complete list of adverse reactions with each drug, please consult the manufacturer's product information.

Note: Bactrim single strength tablets were used in these clinical trials. However, studies have established the bioequivalency of one Bactrim DS tablet with two single strength Bactrim tablets.

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trimethoprim and 400 mg sulfamethoxazole)
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Bactrim DST.M.
(160 mg trimethoprim and 800 mg sulfamethoxazole)
Double Strength tablets

For chronic or frequently recurrent cystitis pyelonephritis due to susceptible organisms.

For longer lasting results in chronic or frequently recurrent cystitis or pyelonephritis

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(80 mg trimethoprim and 400 mg sulfamethoxazole)

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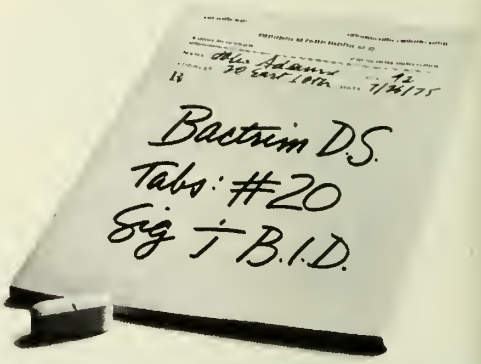
Double Strength tablets



Protocols

While results came from separate studies, protocols were identical with few exceptions:

Equivalencies: Patients selected were asymptomatic with chronic significant bacteriuria or had suffered a recurrence of previously treated symptomatic disease; significant bacteriuria was established as 100,000 or more of same organisms/ml urine in 2 consecutive cultures within 7 days; patient exclusions for reasons of safety or efficacy were identical; the same baseline laboratory studies were made at the same intervals; identical criteria were used to measure success or failure; clear culture was considered as 1000 or fewer organisms/ml urine.

Exceptions: Drug regimens differed (Study #1, two Bactrim tablets b.i.d. or one 500-mg ampicillin capsule q.i.d. for 10 days; Study #2, one 250-mg cephalexin pulvule q.i.d. for 28 days); pretreatment organisms had to be susceptible to ampicillin or cephalexin, but not necessarily to Bactrim.

For more detailed information on the two separate multicenter studies (see previous pages) in which Bactrim achieved better results than ampicillin or cephalexin in maintaining clear cultures, write to:

Professional Services Department
Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Chronic urinary tract infections evidenced by persistent bacteriuria (symptomatic or asymptomatic), frequently recurrent infections (relapse or reinfection), or infections associated with urinary tract complications, such as obstruction. Primarily for cystitis, pyelonephritis or pyelitis due to susceptible strains of *E. coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris* and *Proteus morganii.*

NOTE: The increasing frequency of resistant organisms limits the usefulness of antibacterials, especially in these urinary tract infections. The recommended quantitative disc susceptibility method (*Federal Register,* 37:20527-20529, 1972) may be used to estimate bacterial susceptibility to Bactrim. A laboratory report of "Susceptible to trimethoprim-sulfamethoxazole" indicates an infection likely to respond to Bactrim therapy. If infection is confined to the urine, "Intermediate susceptibility" also indicates a likely response. "Resistant" indicates that response is unlikely.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy; nursing mothers.

Warnings: Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted. **Data are insufficient to recommend use in infants and children under 12.**

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L. E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for children under 12. Usual adult dosage: 1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days.

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) every 24 hours
Below 15	Use not recommended

Supplied: Double Strength (DS) tablets, each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100; Tel-E-Dose® packages of 100. Tablets, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole — bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40, available singly and in trays of 10.

Oral suspension, containing in each teaspoonful (5 ml) the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole; fruit-licorice flavored — bottles of 16 oz (1 pint).

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

How many of your patients know what vitamin A and vitamin C are?

But they do know what vegetables and fruits are.

The foods above have several nutrients in common. The principal ones are vitamins A and C, important for building body resistance to infection. Because citrus fruits, leafy greens, broccoli, carrots, cabbage and others provide these nutrients, these kinds of foods are classified as the Vegetable & Fruit Group in the U.S. Department of Agriculture's Four Food Groups system.

Some physicians counsel patients in terms of nutrients. Which is easier for them to understand—foods or nutrients?

For attractive, color copies of the Four Food Groups guide for your patients, write: Dairy Council of California, Box 28F, Sacramento, CA 95825.

Dairy Council of California

The Four Food Groups—milk, meat, vegetables and fruits, breads and cereals—a practical guide to good nutrition.

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Average weight loss of 2.15 lbs per week compared in clinical studies against a placebo.

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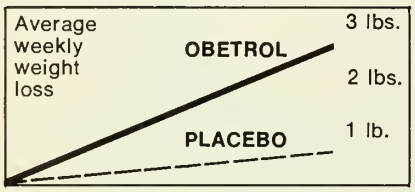
72 CASES 4 WEEKS' RESULTS



Obetrol eases the discomfort of adherence to a restricted diet in individuals who are well motivated to reduce their food intake.

Clinical studies disclose amphetamines to be the most dependable drug in a weight-reduction regimen compared to other anorexigenic agents.

Amphetamines have a significant potential for abuse. In view of their limited short-term anorectic effect and rapid development of tolerance, they should be used with extreme caution and only for limited periods of time in weight reduction programs.

Actions: Amphetamines are sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. The anorectic effect diminishes after a few weeks.

Indications: Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. For patients in whom obesity is refractory to other measures.

Contraindications: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncracy to the sympathomimetic amines. • Agitated states. • Patients with a history of drug abuse. • During or within 14 days following the administration of monoamine oxidase inhibitors, hypertensive crises may result.

Warnings: Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

Precautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen. Amphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Adverse Reactions: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic:* Urticaria. *Endocrine:* Impotence, changes in libido.

Dosage and Administration: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening medication should be avoided because of the resulting insomnia.

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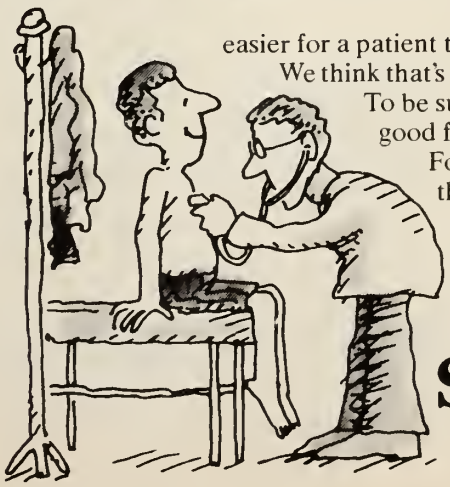

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(Continued from Page 10)

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(Continued on Page 26)

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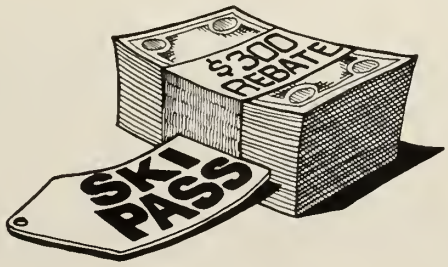

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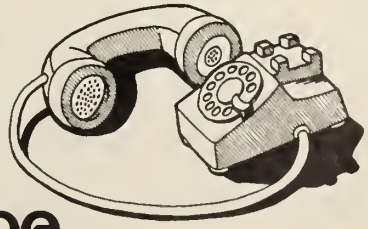

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IN GONORRHEA

INJECTION

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In **Gonorrhea,** the drug regimen of choice is aqueous penicillin G procaine. In uncomplicated cases, administration of 4.8 million units together with 1 gram oral probenecid, given just before injection, is recommended.

Indications: In treatment of moderately severe infections due to penicillin G-sensitive microorganisms sensitive to the low and persistent serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: When high sustained serum levels are required use aqueous penicillin G, IM or IV.

The following infection will usually respond to adequate dosages of intramuscular penicillin G procaine—*N. gonorrhoeae:* acute and chronic (without bacteremia).

For deep intramuscular injection only.

Contraindication: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well-documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents, e.g., pressor amines, antihistamines, and corticosteroids.

Immediate toxic reactions to procaine may occur in some individuals, particularly when a large single dose is administered in the treatment of gonorrhea (4.8 million units). These reactions may be manifested by mental disturbances, including anxiety, confusion, agitation, depression, weakness, seizures, hallucinations, combativeness, and expressed "fear of impending death". The reactions noted in carefully controlled studies occurred in approximately one in 500 patients treated for gonorrhea. Reactions are transient, lasting from 15-30 minutes.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 ml. of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparations should not be used. Antihistaminics appear beneficial in treatment of procaine reactions.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy, discontinue penicillin and take appropriate measures.

If allergic reaction occurs, withdraw penicillin unless in the opinion of the physician, the condition being treated is life threatening and amenable only to penicillin therapy.

When treating gonococcal infections with suspected primary or secondary syphilis, perform proper diagnostic procedures, including darkfield examinations. In all cases in which concomitant syphilis is suspected, perform monthly serological tests for at least four months.

Adverse Reactions: (Penicillin has significant index of sensitization) skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; serum sickness-like reactions, including chills, fever, edema, arthralgia and prostration. Severe and often fatal anaphylaxis has been reported. (See "Warnings.")

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Procaine toxicity manifestations have been reported (see "Warnings"). Procaine hypersensitivity reactions have not been reported with this drug.

Dosage and Administration: Administer only by *deep intramuscular injection,* in upper outer quadrant of buttock. In infants and small children, midlateral aspect of thigh may be preferable. When doses are repeated, vary injection site. Before injection, aspirate to be sure needle bevel is not in blood vessel. If blood appears, remove needle and inject in another site.

Although some isolates of *Neisseria gonorrhoeae* have decreased susceptibility to penicillin, this resistance is relative, not absolute, and penicillin in large doses remains the drug of choice. Physicians are cautioned not to use less than recommended doses.

Gonorrheal infections (uncomplicated)—Men or Women: 4.8 million units intramuscularly divided into at least two doses and injected at different sites at one visit, together with 1 gram of oral probenecid, given just before injection.

NOTE: Treatment of severe complications of gonorrhea should be individualized using large amounts of short-acting penicillin. Gonorrheal endocarditis should be treated intensively with aqueous penicillin G. Prophylactic or epidemiologic treatment for gonorrhea (male and female) is accomplished with same treatment schedules as for uncomplicated gonorrhea.

Retreatment: The National Center for Disease Control, Venereal Disease Branch, U.S. Dept. H.E.W. recommends:

Test cure procedures at approximately 7-14 days after therapy. In the male, a gram-stained smear is adequate if positive; otherwise, a culture specimen should be obtained from the anterior urethra. In the female, culture specimens should be obtained from both the endocervical and anal canal sites.

Retreatment in males is indicated if urethral discharge persists 3 or more days following initial therapy and smear or culture remains positive. Follow-up treatment consists of 4.8 million units aqueous penicillin G procaine, I.M. divided in 2 injection sites at single visit.

In uncomplicated gonorrhea in the female, retreatment is indicated if follow-up cervical or rectal cultures remain positive for *N. gonorrhoeae.* Follow-up treatment consists of 4.8 million units aqueous penicillin G procaine daily on 2 successive days.

Syphilis: all gonorrhea patients should have a serologic test for syphilis at the time of diagnosis. Patients with gonorrhea who also have syphilis should be given additional treatment appropriate to the stage of syphilis.

Composition: Each disposable syringe 2,400,000 units (4-ml. size) contains penicillin G procaine in a stabilized aqueous suspension with sodium citrate buffer, and as w/v approximately 0.5% lecithin, 0.5% carboxymethylcellulose, 0.5% povidone, 0.1% methylparaben, and 0.01% propylparaben. The multiple-dose 10-ml. vial contains per ml. 300,000 units penicillin G procaine in a stabilized aqueous suspension with sodium citrate buffer and approximately 7 mg. lecithin, 2 mg. carboxymethylcellulose, 3 mg. povidone, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben, and 0.14 mg. propylparaben.

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IN SYPHILIS
INJECTION
Bicillin® L-A
(STERILE PENICILLIN G BENZATHINE SUSPENSION) WYETH

Syphilis is preferably treated with penicillin G benzathine, which is also the drug of choice for prophylaxis after exposure. Administration of 2.4 million units (1.2 million in each buttock) usually cures most cases of primary, secondary and latent syphilis with negative spinal fluid.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular penicillin G benzathine.—Venereal infections: Syphilis, yaws, bejel and pinta.

For deep intramuscular injection only.

Contraindication: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens.

Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms including fungi. Take appropriate measures should superinfection occur.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness-like reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high doses of parenteral penicillin.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Dosage and Administration: Venereal infections—

Syphilis—Primary, secondary and latent—2.4 million units (1 dose).

Late (tertiary and neurosyphilis)—2.4 million units at 7 day intervals for three doses.

Congenital—under 2 years of age, 50,000 units/Kg. body weight; ages 2-12 years, adjust dosage based on adult dosage schedule.

(Shake multiple-dose vial vigorously before withdrawing the desired dose.) Administer by **deep intramuscular injection** in the upper outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site. Before injecting the dose, aspirate to be sure needle bevel is not in a blood vessel. If blood appears, remove the needle and inject in another site.

Composition: Units penicillin G benzathine (as active ingredient): 2,400,000 units in 4-ml. single dose disposable syringe. Each disposable syringe also contains in aqueous suspension with sodium citrate buffer, as w/v approximately 0.5% lecithin, 0.6% carboxymethylcellulose, 0.6% povidone, 0.1% methylparaben, and 0.01% propylparaben. 300,000 units per ml.—10-ml. multi-dose vial. Each ml. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. povidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben, and 0.14 mg. propylparaben.

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Refer to: Olinger GN, Po J, Maloney JV Jr, et al: Myocardial revascularization in high-risk coronary patients. West J Med 124:265-271, Apr 1976

THE WESTERN
Journal of Medicine

Myocardial Revascularization in High-Risk Coronary Patients

GORDON N. OLINGER, MD; JONATHAN PO, MD; JAMES V. MALONEY, JR., MD; DONALD G. MULDER, MD, *and* GERALD D. BUCKBERG, MD, *Los Angeles*

It is recognized that postoperative mortality, infarction and the need for inotropic support are increased following myocardial revascularization in high-risk patients. Operations were carried out in 57 such patients in whom one or more of the following factors were present: ventricular dysfunction—ejection fraction less than 0.4 (17), unstable (8) or preinfarction angina (29), evolving infarction (8), recent infarction (less than two weeks before) (5) and refractory ventricular tachyarrhythmia (4). Combined risk factors were present in nine patients. The following principles were utilized to minimize ischemic injury: (1) avoidance of prebypass hypertension and hypotension, (2) avoidance of extreme hemodilution, (3) avoidance of ventricular fibrillation, (4) maintenance of beating empty heart, when possible, (5) the limiting of ischemic periods to less than 12 minutes (hypothermia 32°C) and (6) repaying myocardial oxygen debt with total (vented) *bypass, when necessary. The following results were obtained: inotropic support was required in five patients (9 percent), "new" postoperative infarction occurred in five patients (9 percent) and one patient died (2 percent). These results are comparable to those reported in good-risk patients, and indicate that optimal myocardial protection will allow safe revascularization in a high-risk patient.*

THE INCIDENCE of postoperative mortality, myocardial infarction and depressed cardiac performance requiring pharmacologic or mechanical circulatory support is reportedly increased in high-risk patients in whom coronary revascularization is carried out (Table 1). This group of patients includes those with ventricular dysfunction (ejection fraction less than 0.40), serious ventricular tachyarrhythmias, preinfarction angina, evolving myocardial infarction and recent infarction with signs of extension. We believe that the increased morbidity and mortality following coronary bypass surgical procedures in these patients is (1) frequently caused by ischemic myocardial damage during operation and (2) can be minimized significantly if careful attention is directed toward principles of myocardial protection.

From the Division of Thoracic Surgery, Department of Surgery (Drs. Olinger, Maloney, Mulder and Buckberg) and the Department of Radiology (Dr. Po), University of California, Los Angeles, School of Medicine.

Submitted August 1, 1975.

This study was supported by grants-in-aid from the Beaumont Foundation, the Wilbur May Foundation, Frank W. Clark, Jr. Charities, and the Blalock Foundation. The experimental work on which the clinical study was based was supported by grants-in-aid from the United States Public Health Service.

Reprint requests to: Gerald Buckberg, MD, Division of Thoracic Surgery, UCLA School of Medicine, Los Angeles, CA 90024.

TABLE 1.—*Reported Mortality After Revascularization in High-Risk Patients (1972-1974)*

Category	*Range (Percent)*	*Deaths/ Total Patients (Percent)*
Ventricular dysfunction (ejection fraction <0.40)	9-33[1-4]	12
Refractory ventricular arrhythmia	13-30[5,6]	22
Preinfarction angina	0-23[7-10]	9
Evolving infarction	5-38[11-14]	14
Recent infarction (<four weeks)	0-80[15-18]	27

Clinical Material

Coronary revascularization in 57 consecutive high-risk patients was carried out at the University of California, Los Angeles, Medical Center in the past 33 months. Nine patients had combined risk factors. Operation was done as an emergency procedure in 51 of these patients.

Ventricular Dysfunction

Ventriculography, at the time of cardiac catheterization, showed impaired contractility (ejection fraction less than 0.40) in 17 patients. The mean ejection fraction was 0.28 ± 0.08 S.D. Six patients in this category were the only ones in whom coronary revascularization was done as an elective procedure.

Refractory Ventricular Tachyarrhythmia

Repeated episodes of ventricular tachycardia or fibrillation or both were present in four patients. The refractory arrhythmia developed within two weeks of acute myocardial infarction in two patients, within eight weeks in one patient, and during repeated bouts of preinfarction angina in another. The ejection fraction was less than 0.40 in three patients in this category.

Preinfarction Angina

In 29 patients, coronary revascularization was done primarily because of preinfarction angina. In each patient there developed (1) pain at rest, (2) prolonged angina pectoris (more than 20 minutes), (3) incomplete relief of pain by coronary vasodilators—nitroglycerin, isosorbide dinitrate (Isordil®)—or propranolol and (4) ST depression (greater than 2 mm) and T wave changes on the precordial electrocardiogram. Emergency cardiac catheterization and coronary revascularization were carried out for these indications. Patients in whom there had been recent changes in anginal syndrome were not considered in this high-risk category. Combined risk factors were present in seven of these patients. (Ventricular dysfunction occurred in five patients and refractory tachyarrhythmia in two.)

Evolving Infarction

Coronary revascularization was carried out in eight patients because of evolving acute myocardial infarction. This was defined as chest pain at rest, unrelieved by coronary vasodilators and characterized by electrocardiographic findings of ST segment elevation (greater than 2 mm) with reciprocal depression and elevation of serum transaminase to greater than 40 units and creatine phosphokinase (CPK) to greater than 200 units. In each patient coronary arteriography had been done before acute infarction. Acute infarction developed in one patient one week after coronary revascularization for preinfarction angina and in this patient an occlusion of a single left anterior descending coronary artery bypass graft was known to exist. Cardiogenic shock was not present in any patient.

Recent Myocardial Infarction

In five patients coronary revascularization was carried out because of the development of recurrent chest pain, associated with progression of the ST and T wave changes of acute infarction within two weeks after myocardial infarction.

Operative Technique

Before Bypass

At the completion of cardiac catheterization, a Swan-Ganz catheter was usually placed into the pulmonary artery to allow monitoring of pulmonary artery wedge pressure during induction of general anesthesia. Under local anesthesia (1 percent xylocaine), a Teflon® catheter was placed percutaneously into the radial artery to monitor arterial blood pressure. Intravenous infusions of isoproterenol and nitroprusside were prepared before induction of general anesthesia to treat hypotension and hypertension. Anesthesia was induced with intravenous administration of barbiturate, narcotic and paralytic agents and maintained with minimal doses of nitrous oxide and enflurane. Prebypass hypertension was treated with nitroprusside infusion if pulmonary artery wedge pressure increased above values recorded before anesthesia, or ST and T wave changes were noted on electrocardiograms. Decisions regarding treatment of hypotension were based upon changes in

pulmonary artery wedge pressure. If wedge pressure was less than 18 mm of mercury, volume (plasma) was infused. If hypotension was associated with the rise in pulmonary wedge pressure, the inhalation anesthetic agent was reduced in concentration or discontinued. If this did not produce an immediate rise in blood pressure, then isoproterenol was administered intravenously.

During Bypass

Cardiopulmonary bypass was instituted by diverting venous return from the right atrium with a large single drainage cannula and returning oxygenated blood into the femoral artery. The bypass circuit (Bentley) was primed with 1,000 ml of whole blood and 1,500 ml of Ringer's lactate. The average hematocrit value during bypass was 32 percent. Body temperature was maintained at 89.6°F (32°C). Perfusion pressure was kept between 75 and 100 mm of mercury by adjusting the rate of perfusion and administering phenylephrine hydrochloride after flows in excess of 80 ml per kg of body weight per minute or a maximum of 5 liters per minute failed to increase perfusion pressure.

A polyethylene catheter was placed into the left atrium through the right superior pulmonary vein. The left ventricle was decompressed in *all* patients, most often by introduction of a vent through a stab wound into the left ventricular apex. The adequacy of left ventricular venting was assessed by monitoring left atrial pressure; the vent was readjusted if pressure rose above zero mm of mercury.

All coronary and aortic anastomoses were done during bypass. Coronary anastomoses were always carried out first. The aorta was cross-clamped in order to create a quiet operative field for all circumflex, most left anterior descending and many right coronary anastomoses. A continuous suture technique (6-0 prolene) was used and most anastomoses were completed within 12 minutes. The cross clamp was released after each anastomosis was completed and ventricular fibrillation, when present, was reverted immediately. The aorta was clamped tangentially in order to make the proximal anastomosis (continuous suture with 5-0 prolene). This insured continuous coronary perfusion with the heart in a beating nonworking state so that the myocardial oxygen debt (incurred during ischemic arrest) was repaid while proximal anastomosis was accomplished. Many right coronary anastomoses and some left anterior descending anastomoses were done while the empty heart beat and antegrade and retrograde flow from the proximal and distal vessel were controlled by tension on sutures previously placed beneath the vessel.

TABLE 2.—*Morbidity and Mortality After Revascularization in 57 High-Risk Patients (UCLA, 1972-1974)*

	Patients	*Percent*
Inotropic support	5/57	9
"New" infarction	5/57	9
Deaths	1/57	2

Cardiopulmonary bypass was discontinued initially with the vent left in place. Total bypass was reinstituted if left atrial pressure exceeded preoperative values or if arterial blood pressure was less than 100 mm of mercury with left atrial pressure greater than 20 mm of mercury. The left ventricle was decompressed through the vent and arterial pressure was raised to 100 mm of mercury by increasing the flow rate through the oxygenator and by administering phenylephrine hydrochloride into a perfusion circuit if the flow rate exceeded 80 ml per kg of body weight per minute. Total bypass was prolonged for a minimum of 15 minutes when myocardial performance was considered impaired.

Results

The results are shown in Table 2.

Postoperative Circulatory Support

In 5 of 57 patients (9 percent) circulatory support with inotropic drugs was required in the postoperative period. Clinical indications included (1) arterial blood pressure less than 100 mm of mercury which did not increase when left atrial pressure was raised to 20 mm of mercury, (2) urine output less than 25 ml per hour, (3) metabolic acidosis and (4) peripheral vasoconstriction and cyanosis. In two patients in whom inotropic support was required, revascularization was carried out for evolving myocardial infarction (one of these died) and one patient was operated upon for extension of a recent infarction (one week). In the other two patients, severe left ventricular dysfunction was present with ejection fractions of 0.12 and 0.25.

"New" Postoperative Infarction

Postoperative infarction was defined as development of persistent new Q waves or loss of a preexistent precordial R wave progression, or both. In five of 57 patients (9 percent) this

complication developed. In three of these patients, revascularization had been carried out during an evolving infarction (ST elevation in precordial leads), but Q waves did not appear on electrocardiograms until the postoperative period. Operation was carried out in a fourth patient for recurrent chest pain occuring one week after an acute infarction. No Q waves developed postoperatively, but serum CPK was more than 2,000 units. Postoperative infarction developed in the fifth patient after revascularization for preinfarction angina.

Deaths

One of 57 patients (2 percent) died after coronary revascularization. This patient was operated on during the early phase of our experience, had an evolving myocardial infarction and died in the operating room. Blood pressure was extremely labile in the preoperative period and was not controlled pharmacologically. Cardiac performance was impaired after discontinuation of bypass and rather than prolonging *total* bypass as is our current practice, we proceeded directly to inotropic support.

Discussion

The incidence of postoperative myocardial depression requiring pharmacologic or mechanical circulatory support, of infarction and of death in these 57 consecutive high-risk patients is comparable with that reported after elective revascularization in patients with good ventricular performance.[1-19] We believe the low morbidity and mortality achieved in these patients is due to careful attention to principles of myocardial protection during revascularization. These principles are drawn from previously known fundamentals of coronary physiology and from experimental studies done recently in our laboratory.[20-28]

The performance of the heart following discontinuation of bypass after revascularization is determined by the extent of ischemic injury incurred during the prebypass interval and during bypass and by how well the oxygen debt was repaid before the heart was called upon to resume its function.

In a normal heart, without coronary artery disease, myocardial oxygen supply (coronary flow and oxygen content) is maintained at a level sufficient to meet cardiac oxygen demands by the mechanism of coronary autoregulation. Temporary coronary artery occlusion, which interrupts cardiac oxygen supply, causes myocardial hypoxia and coronary dilatation. A pronounced increase in coronary flow (reactive hyperemia) usually follows release of the occlusion. As a result the oxygen debt which had been incurred when blood supply was interrupted is repaid by increased coronary flow while perfusion pressure is constant. The extent of the oxygen debt is determined by the oxygen requirement (work done) while flow is interrupted, and peak flow during reactive hyperemia is determined by the coronary driving pressure.

We presume that patients in whom *elective* coronary revascularization is carried out retain some degree of coronary vasodilator reserve capacity so that adequate coronary blood flow is maintained despite minor increases in oxygen requirements or reductions in coronary driving pressure. In these patients a greater degree of coronary vasodilatation is present at rest, in order to insure oxygen delivery to the myocardium in the area supplied by a stenotic vessel (where perfusion pressure is lowered by the atherosclerotic plaque). We believe, however, that in such patients some ability is retained to dilate coronary arteries in response to increased oxygen demands or reduced perfusion pressure, and that consequently, the oxygen debt following temporary coronary occlusion would likely be repaid by reactive hyperemia. A *high-risk* patient, on the other hand, is far more vulnerable to ischemic damage because his coronary vascular bed may already be maximally dilated; the ability to maintain by reactive hyperemia adequate myocardial perfusion if oxygen demands increase or factors affecting oxygen delivery are reduced is lost. Ischemia can develop as a result of minor imbalances between myocardial oxygen requirements and supply.

Principles of Myocardial Protection

We adhered to several principles of myocardial protection during coronary revascularization in patients presented in this review.

- *Avoid prebypass hypotension and hypertension*

Since oxygen extraction by the heart is almost complete, the volume of coronary blood flow is the principal determinant of oxygen delivery. With vasodilatation, assumed to be present to a near maximal degree in all high-risk coronary patients, flow is determined by the coronary driving pressure (difference between coronary blood pressure and left ventricular diastolic blood pres-

sure). Reduction in driving pressure causes decreased coronary flow. Such hypotension occurs either because myocardial contractility is impaired or because ventricular filling (preload) is inadequate. We monitor pulmonary artery wedge pressure to assess left sided filling pressure. If the wedge pressure is low we administer volume; if it is high we use an inotropic drug.

Hypertension is also detrimental to the heart because it raises myocardial oxygen requirements by increasing wall tension (the product of pressure and internal radius) and by increasing pressure work. Although coronary diastolic pressure may rise with hypertension, coronary flow may not increase sufficiently to meet oxygen demands. Furthermore, left ventricular diastolic pressure, which acts as a counterforce to coronary flow by reducing coronary driving pressure, is also increased when afterload is raised. We have been impressed that severe electrocardiographic ischemia develops during prebypass hypertension. With intravenously administered nitroprusside, blood pressure is readily controlled and electrocardiographic changes of ischemia are reversed.

- *Avoid extreme hemodilution*

We have produced ischemia experimentally when hemoglobin levels are reduced to less than 5 grams per 100 ml without coronary obstruction, and with hemoglobin levels less than 10 grams per 100 ml if myocardial oxygen requirements are increased.[25,26] We believe that in a high-risk coronary artery patient with an already impaired myocardial oxygen supply and near maximum coronary vasodilatation, production of acute normovolemic anemia and reduced blood oxygen content by withdrawal of blood and replacement with colloid or crystalloid is contraindicated in the prebypass period. We use moderate hemodilution (hematocrit 32 percent) to save blood.

Most bypass operations are carried out with some degree of hypothermia, which we, and others, have recently shown limits coronary vasodilator reserve capacity.[29] Since the coronary arteries are maximally dilated and perfusion pressure is already low beyond coronary obstructions, extreme reductions in blood oxygen content may prevent adequate oxygen delivery during bypass. It may also preclude full repayment of the oxygen debt which follows the inevitable periods of ischemia incurred while carrying out anastomoses.

- *Avoid ventricular fibrillation*

We believe that ventricular fibrillation should be avoided during myocardial revascularization. Our studies show that the myocardial oxygen requirements during ventricular fibrillation are only slightly less than those of a beating working heart.[22] Although fibrillation provides a quiet operative field the coronary artery must nevertheless be occluded in order to carry out the anastomosis, and the region of the myocardium supplied by it is made more ischemic.

Results of studies by Baird, and those in our laboratory, have shown that the blood supply to the myocardium cannot be maintained adequately if perfusion pressure is reduced while the heart is allowed to fibrillate.[27,30] The fibrillating heart becomes ischemic when perfusion pressure is lowered to 50 mm of mercury (a perfusion pressure in general use during cardiopulmonary bypass) both at normothermia and hypothermia. We believe a 50 percent pressure drop across a region of severe coronary stenosis is not uncommon in clinical coronary artery disease, so that inadequate perfusion of the distal myocardium might be expected to occur during ventricular fibrillation even when perfusion pressure is maintained at 100 mm of mercury in the aortic root. As a result, not only is blood supply to the area undergoing revascularization interrupted, but the remaining myocardium is perfused inadequately. The ischemia of fibrillation is even more severe if it is maintained with a continuing electrical stimulus, or if allowed to persist spontaneously in hypertrophied hearts.[21,22]

- *Maintain beating empty heart, when possible*

Our experimental studies and clinical experience indicate that the heart is protected against ischemic injury best when it is allowed to beat while being continually perfused with oxygenated blood.[21] A beating empty heart (vented) consumes approximately a third as much oxygen as a working heart and half as much oxygen as a fibrillating heart. We maintain the heart in the beating empty state as much as possible with perfusion pressure at 80 to 100 mm of mercury. For technical reasons, however, coronary anastomoses are cumbersome in the beating heart. We use intermittent periods of ischemia to provide a quiet operative field, limit ischemic periods and allow adequate repayment of the oxygen debt. The oxygen requirements of an arrested heart are only 30

percent less than those of a beating empty heart (3 versus 2 ml per 100 grams per minute)[31] and ischemic arrest provides distinct technical advantages. The supply/demand discrepancy in the area supplied by the vessel undergoing revascularization is therefore reduced when the heart is stopped during the time of anastomosis.

Coronary revascularization is carried out during mild perfusion hypothermia (32°C), which lowers oxygen requirements during the period of arrest. Occasionally, we use topical hypothermia for added protection. The effects of topical hypothermia on the distribution and adequacy of coronary flow have yet to be evaluated. Using these techniques, most anastomoses can be accomplished within 12 minutes, a time arbitrarily chosen as safe.

After release of the the aortic cross clamp, we believe it essential to allow a comparable period for repayment of the oxygen debt. Aortic-vein graft anastomoses are done during this period of repayment. The heart is immediately defibrillated after the cross clamp is removed so that the oxygen requirements are reduced while coronary reactive hyperemia and repayment are occurring.

- *Prolongation of total bypass with venting*

Patients in whom successful revascularization has been accomplished should be expected to have an improved rather than depressed myocardial performance following discontinuation of bypass. If depressed myocardial performance occurs, the ischemic injury occurring before and during bypass has offset the improvement resulting from revascularization. This suggests that the oxygen debt incurred during bypass was not repaid before the heart was called upon to resume its function.

We believe that immediate resumption of bypass in the failing myocardium is a far better alternative than institution of inotropic support. The heart on total bypass is restored to the beating empty state where oxygen requirements are low. For this reason, we frequently leave the left ventricular vent in place so that even the small amount of flow in the bronchial system can be diverted and the isometric work of the heart reduced. We assess the adequacy of venting by insuring that left atrial pressure is reduced to zero. Adequate venting reduces wall tension and eliminates impedance to myocardial perfusion caused by increased left ventricular diastolic pressure.[23] If a poorly functioning heart is allowed to do external work (partial bypass) its oxygen requirements are increased, with a high left ventricular diastolic pressure impeding subendocardial flow. Blood supply to a vented bypassed heart can be maximized by raising aortic pressure (increasing pump flow or adding a peripheral vasoconstrictor) to approximately 100 mm of mercury. Resumption of total bypass for short periods (15 to 20 minutes) will frequently repay the oxygen debt satisfactorily and prevent the need of postoperative inotropic support.

Balloon counterpulsation is used by some to optimize the supply/demand relationship when patients have difficulty sustaining effective cardiac action after bypass. This maneuver is most effective only with a regular rhythm and, although it reduces oxygen requirements, the external work of the myocardium is not eliminated. Resumption of total bypass offers a better method of augmenting coronary blood supply while simultaneously reducing oxygen requirements.

Summary

Coronary revascularization was carried out in 57 consecutive patients in the high-risk category (ventricular dysfunction, ventricular tachyarrhythmia, preinfarction angina, evolving myocardial infarction and recent myocardial infarction with extension). The incidence of postoperative morbidity and mortality was comparable to that in cases of elective revascularization. We believe these results are directly attributable to careful attention to principles of myocardial protection during operation.

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Treatment of Infertile Patients with Adequate or Slightly Diminished Endogenous Estrogen with a Lack of LH Surge

In these patients, we have utilized either estrogen in the form of ethinyl estradiol (Estinyl®) —0.02 mg daily for three days, then twice daily for three days, then three times daily for three days—or clomiphene citrate—50 mg daily for five days and, if unsuccessful, 100 mg daily for five days. In about 85 percent of such patients, ovulation will be successfully induced, with the luteinizing hormone (LH) surge occurring four to six days after the last dose of clomiphene. If ovulation is not induced by these methods, human chorionic gonadotropin (HCG), 10,000 IU, is given four days after the last dose of clomiphene.

In regard to those patients who have low endogenous estrogen and low follicle-stimulating hormone (FSH) and no LH surge, administration of clomiphene in these patients is either increased in a daily dosage of 200 mg daily for five to seven days or it is given in a sequence of 100 mg daily for ten days. The administration of clomiphene to these patients frequently evokes release of FSH sufficient to produce follicular maturation, but LH burst is not, unfortunately, obtained; therefore, HCG (10,000 IU) is given four days after the last dose of clomiphene. The HCG acts in the same fashion as LH and is effective in rupturing the mature follicle.

If the above sequence is not effective in securing ovulation, or if apparent ovulation is produced for five to six consecutive cycles and pregnancy does not occur, we have, during the last two to three years, utilized a sequential regimen of clomiphene (giving 100 mg daily for seven days) followed by Pergonal® (75 IU of FSH, 75 IU of LH in each ampule), giving two ampules daily for 4 to 6 additional days. After a 4 plus fern test is obtained in the cervical mucus, a 24-hour urine collection is assayed for total estrogen. If the total estrogens in the urine do not exceed 100 micrograms, we feel safe in administering the HCG (10,000 IU after a 24-hour interval of no therapy). Usually, after eight ampules (two daily for four days) we give a step-down dose of one ampule daily for two days, skip one day, then administer the HCG. In order to prevent premature demise of the corpus luteum, HCG is given in a dose of 2,000 IU, four days after the first HCG. This sequence has resulted in 25 pregnancies in 70 treated patients.

—ROBERT W. KISTNER, MD, *Boston*

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Tattoo Removal by Split Thickness Tangential Excision

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Split thickness tangential excision is a simple means of tattoo removal with very acceptable cosmetic results. The technique has several advantages. (1) The depth of skin removal may accurately be controlled as the tattoo pigment is excised with a dermatome. The major portion, if not all of the remaining pigment, is extruded and sloughs with the crust. (2) Scar formation, if it occurs at all, is negligible. (3) No donor site is created. (4) The procedure may be carried out rapidly without admitting patients to hospital, is inexpensive for patients and conserves time for physicians.

THE PROBLEM of tattoo removal is far from new. In the Book of Leviticus (XIX:28), Moses was commanded, "Ye shall not . . . tattoo any marks upon you." Unfortunately for plastic surgeons, this advice has not been followed, and tattooing remains a relatively popular means of identification and a fashionable mode of social expression among certain groups. Bromberg suggested that tattooing is frequently a sign of emotional immaturity.[1]

All methods of tattoo removal involve some element of destruction of the skin to ablate pigment design. Pigment depth varies with the technique used. The pigment in a professional tattoo is injected with an automatic reciprocating needle at a constant depth, usually in the superficial dermis. Various amateur techniques that employ sharpened needles, with or without thread and covered with india ink or shoe polish, offer little control over the depth of pigment deposition. The pigment frequently is deposited in the deep dermis or in the subcutaneous tissue. Obviously, greater success in removing the tattoo can be achieved when the pigment lies superficially.

The approach to tattoo removal may be divided into two categories: nonsurgical methods utilizing locally applied chemical or physical agents and surgical techniques.

Nonsurgical Methods

Counter-tattooing with tannic acid in conjunction with other topically applied agents has been used extensively by tattoo artists for many years as a means of altering unwanted tattoos. A recent modification of this procedure has been described.[2]

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Sodium chloride was first reported as an abrasive for use in tattoo removal in 1935.[3,4] In 1971, Crittenden[5] coined the term "salabrasion" to describe his refinement of the technique in which crystalline salt is rubbed over the tattooed area with a moist sponge. When delivered to the dermal tissues, the salt solution is thought to act not only as an abrasive but also as a stimulant to pigment phagocytosis by macrophages.[6] The pigment-laden macrophages migrate to the wound surface where they are removed with the dressing changes.

Numerous physical agents have been employed in the ablation of tattoos. Use of boiling water, hot irons and electrocoagulation are effective by causing thermal injury to superficial layers of skin. Finsen light reportedly speeds the normal fading process.[7] Lasers have been used to vaporize and to disburse the particles of pigment, although their routine clinical use has not been recommended.[8]

Both physical and chemical agents act by destroying varying depth of skin. With subsequent exfoliation or sloughing, tattooed pigment is removed. The principal difficulty with the use of chemical and physical agents is depth control. Deep dermal injury or full-thickness loss with attendent scarring may result.

Surgical Methods

Surgical techniques for tattoo removal have generally been the most popular with physicians. Dermabrasion is widely used because of its simplicity and generally satisfactory results. In the first description of this technique, the tattooed area was abraded until all pigment was removed, with deep dermal injury and frequent excessive scarring resulting. Recent refinements in the technique have led to advocacy of superficial abrasion and *partial* pigment removal, with reliance upon the phagocytic response to extrude the remainder of the pigment in the crust[9] or to carry away the pigment through the lymphatic system.[10] However, pigment removal is often incomplete, and repeated dermabrasions are required.

Excision of the tattoo with simple wound closure has long been a popular and acceptable method for removing small tattoos. Indeed, in dealing with small tattoos, it is probably the method of choice. Staged excision has been used for removing those tattoos that cover large areas. However, after aggressive excision and closure under tension, the scar often spreads and there is an undesirable cosmetic result.

A sure method of removing all pigment is full-thickness excision of the tattoo and coverage of the defect with a split-thickness skin graft. However, subsequent hyperpigmentation of the graft and scarring at the margins may compromise the cosmetic result.

Tattoo removal using the method and dermatome of Reese was described by Bunke and Conway.[11] The pattern of the tattoo is painted with cement, and a thick split-thickness graft is taken. In this way most, if not all, of the pigment is removed. A graft of similar thickness from another site is then used to cover the bed. The remaining pigment can be partially obscured by the opalescent nature of the thick graft. Bailey[12] has also recommended tangential excision with a Watson-Braithwaite knife, followed by skin grafting.

With dermabrasion, pigment removal is often irregular and depth of abrasion difficult to control. In techniques in which grafting is used, a second wound is created and therefore the likelihood of scar formation is increased.

We have had success with a simple method in which the tattoo is excised tangentially with a power-driven oscillating dermatome. The wound is allowed to heal like a split graft donor site, precluding the necessity of an additional graft procedure.

Method

The area is shaved and prepared with providone-iodine. Next, a solution of 0.5 percent lidocaine with 1:200,000 epinephrine is infiltrated into the skin to elevate the exact area of pigment to be removed. An intermediate split-thickness portion of the skin is then excised with the power-driven oscillating dermatome. The thickness of the tangentially excised tattoo is determined by the location of the tattoo; that is, very thin sections are taken for sites such as the volar forearm, and thick grafts are removed in areas such as the trunk. The wound is then covered with a single layer of fine mesh gauze and wrapped in a bulky gauze dressing. The following day the bulky dressing is removed, and the wound is allowed to form a crust with the fine mesh gauze in place. With spontaneous separation of the crust and fine mesh gauze, the wound is fully epithelialized similar to a donor site. Pigment that remains after excision of the specimen with the dermatome is often found adherent to the fine mesh gauze and crust.

Results

This method has been used in 24 patients. In all, the pigment was sufficiently removed to prevent recognition of the original design, and the results were considered to be cosmetically acceptable. In 14 tattoos, all pigment was removed, as illustrated in Figure 1. In four patients, a second procedure was required to complete the tattoo removal. The remaining six patients were satisfied with the ablation of the word or design of the tattoo although some pigment remained. There were no wound infections or full-thickness losses.

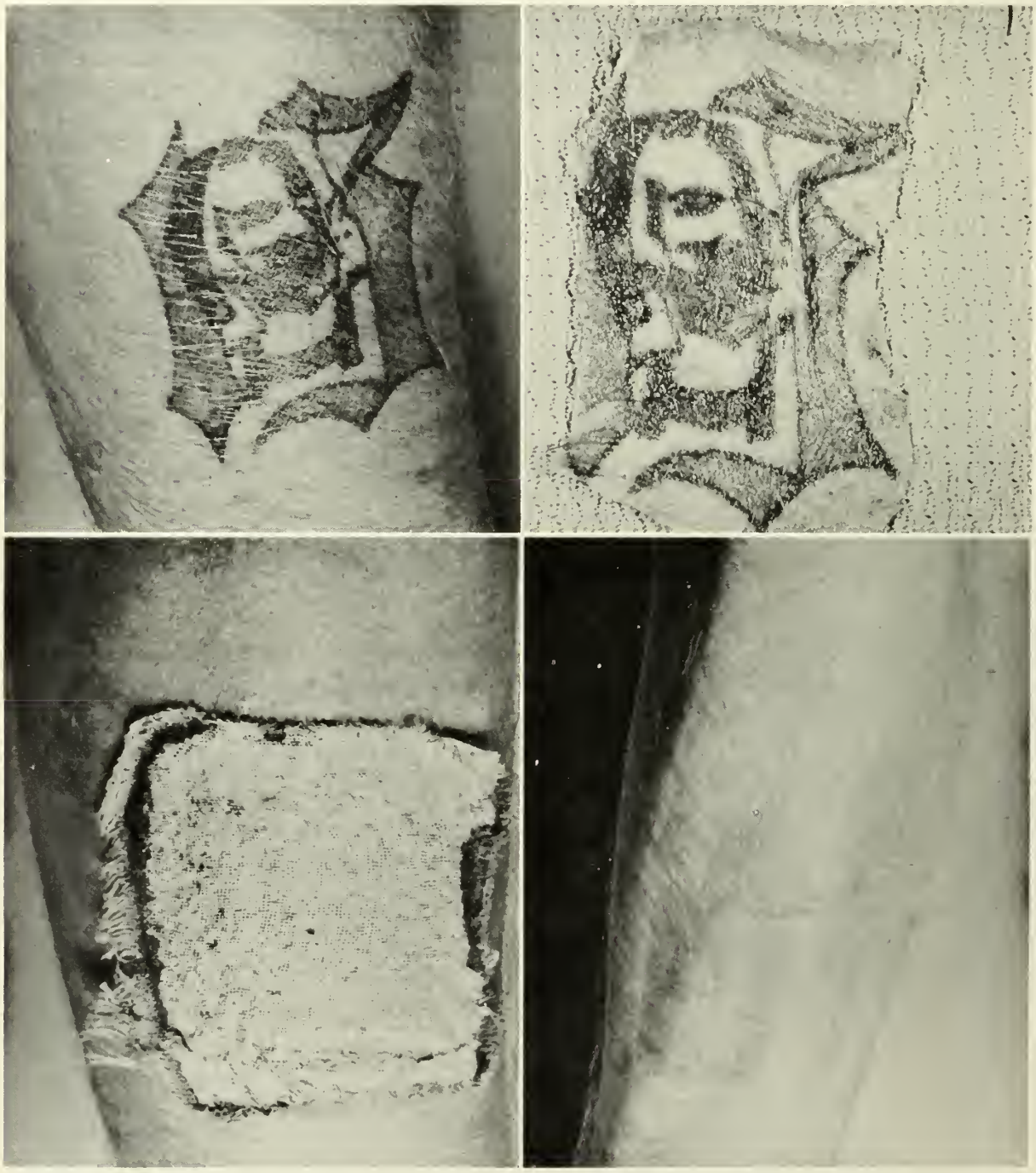

Figure 1.—Upper Left, preoperative view of forearm tat as a donor site. **Lower Right,** tangentially excised area split-thickness graft taken with the Brown dermatome foltoo. **Upper Right,** tangentially excised moderate depth mented area. **Lower Left,** wound treated conventionallylowing injection of tattoo with lidocaine to elevate pig- 6 weeks postoperatively.

Discussion

Simple tangential partial-thickness excision provides an alternative means of rapidly removing tattoos. Dermabrasion, in our experience, has generally yielded satisfactory results. However, with dermabrasion considerable time is required and if the abrasion is too deep and done unevenly, dermal injury may result in conspicuous scar formation. We continue to use excision and primary closure for removing small tattoos in patients with sufficient skin mobility to permit closure with minimal tension. Salabrasion has been used with success by some authors.[3-6] When done by a physician and the proper depth is achieved, results can be excellent although, again, the procedure is time-consuming. When a patient does the procedure himself, results are generally less than optimal. A well-motivated patient seen in our clinic had been too vigorous in his attempts at salabrasion, and the abraded site healed with substantial scar formation. Furthermore, pain is produced with the abrasion because the salt most often does not provide sufficient anesthesia, as has been reported. Although subsequent salabrasions may be done, patients usually request an alternate method.

It has been suggested that salt solution acts as a stimulus to pigment phagocytosis. Similarly, other authors have noted that active pigment is phagocytized by macrophages that migrate to the wound surface.[9] Boo-Chai[10] theorized that trauma induces accelerated pigment removal by lymphatics. It seems reasonable that this phenomenon is a consequence of a general inflammatory response and occurs regardless of the initial traumatic stimulus, whether it be salt, dermabrasion or tangential excision.

Tangential excision, as described, removes all or a large portion of the pigments, as do other methods. Tangential excision also appears to act as a stimulus to the inflammatory response. The advantages of this technique are that it is easier to control the depth of skin removal with the dermatome, and the procedure may be completed more rapidly than with abrasive techniques. Others have found unacceptable scarring with tangential excision without graft coverage.[12] It should be pointed out, however, that in the study with this finding, multiple excisions had been carried out until all pigment was removed. Such a deep dermal wound frequently results in excessive scarring. Time was not allowed for subsequent inflammatory pigment removal postoperatively.

Excision of the tattoo with the oscillating dermatome followed by coverage with a split-thickness graft was in the past a popular method.[11,12] With this overgrafting technique, a second wound is created and this often necessitates admission of the patient to hospital. It should also be noted that contraction and hyperpigmentation of the graft can result.

In the technique described, the superficially excised area heals without an overlying graft, like a donor site. It is not necessary to take skin from another site to cover the defect. Because the tangential excision is superficial, there is seldom any apparent scarring, and the remaining pigment is usually extruded in the crust. The depth of epidermal excision is more precisely controlled with the dermatome than with abrasion techniques, and the procedure is carried out far more rapidly. In our experience, the results have proved superior to other methods.

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Neurological Complications of Endocarditis in Persons Taking Drugs Intravenously

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A study was made of 46 cases of endocarditis in persons known to take drugs intravenously. Findings included significantly lower ages for those patients in whom infections were right-sided. The neurological complication rate was 39 percent overall and 58 percent in the left-sided group. Neurological complications are unusual in right-sided infection. In about a third of those with neurological complications there were sensorial changes without focal signs. Despite a high mortality, neurological complications in Group D streptococcal endocarditis were relatively infrequent. One case is presented in which a foreign body may have contributed to the formation of the embolic material. The clinical and neuropathological features encountered are compared with those reported in persons with endocarditis who were not addicts. The review indicates that neurological complications in nonaddicts and in addicts are similar in type but are more common and severe in addicts.

INFECTIOUS ENDOCARDITIS in persons using drugs intravenously has come to be a well-recognized clinical problem in most city hospitals. The high mortality and high morbidity noted in reviews[1-4] published between 1967 and 1970 have been attributed in part to a bias created by reporting particularly severe cases or by using autopsy records as a source of some cases.[4] More recent series have noted fewer fungal and Gram-negative cases,[5] a higher percentage of right-sided infection[6] and a more favorable prognosis.[7]

The present report concerns the neurological complications seen in drug-related endocarditis from 1966 to 1972 in a city hospital, a university hospital and a Veterans Administration hospital in San Francisco. Including all of the cases filed in the medical record departments in which the diagnoses were clinically and bacteriologically

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TABLE 1.—*Organism, Number of Complications and Mortality in 46 Cases of Endocarditis in Drug Addicts*

	Organism	Neurological Complications	Mortality
Right-sided			
Staphylococcus aureus	14	0	0
Serratia marcescens	1	1	1
Left-sided			
Group D Streptococcus	9	1	4
Viridans Streptococcus	9	3	2
Candida albicans	8	4	3
Staphylococcus aureus	5	5	2
Serratia marcescens	4	4	4
Microaerophilic streptococcus	1	1	1
Pseudomonas aeruginosa	1	1	1
Mixed	6	4	3

TABLE 2.—*Clinical Presentation of Patients with Neurological Signs*

	Cases	Mortality
Focal hemisphere signs with or without sensorium changes	9	5
Sensorium changes alone ("meningoencephalitis")	5	3
Brain stem sign of transtentorial herniation	2	2

TABLE 3.—*Types of Neurological Complications*

	Number	Mortality
Single infarct	6	3
Multiple infarcts	4	3
Mycotic aneurysm (ruptured)	2	1
Microabscess	1	1
Microabscess and a single infarct	1	1
Abscesses, infarct, mycotic aneurysm	2	2

confirmed, the results of this study are closer to those of the earlier reports than to the later series in that the morbidity and mortality were high, and Gram-negative and fungal organisms were encountered relatively frequently. The incidence and types of neurological complications are compared with those reported in recent reviews of neurological complications of endocarditis in nonaddicts.[8-10] The results are combined when possible with information supplied by recent series of endocarditis cases in addicts.[4-7] Case material before 1967 has been covered in reviews, and individual earlier references can be obtained from these reviews.[1-3]

Results

In all, 46 cases of endocarditis were seen in 41 drug users in the seven-year period. Table 1 outlines the organisms, sites of infection, mortality and incidence of neurological complications in these cases.

The endocarditis was exclusively right-sided in 15 cases, left-sided in 29 cases and bilateral in 2 cases. The age of 26.2±1.2 years (mean±SEM) of those with right-sided involvement was significantly lower than that of those patients with left-sided involvement (35.3±1.8). The sex ratio was about one to one in the right-sided group, but the ratio of men to women was nearly six to one in the left-sided group. The pulmonic valve was not involved in any of these cases. Of the left-sided cases, the aortic valve was involved in 17 cases, the mitral in 12 cases and both valves in 2 cases. The overall mortality in the 41 patients was 37 percent. Of those with left-sided infection, the mortality was 54 percent.

Neurological complications were present in 16 patients. This constitutes 39 percent of the entire group and 58 percent of the left-sided group. The average age of 33.6 years was similar to the average age of the left-sided group. The mortality of 69 percent was higher than the mortality of the entire left-sided group. The male preponderance of 15 to 1 was also greater. The endocarditis was confined to the mitral valve in six, aortic valve in five and tricuspid in one. The tricuspid and aortic valves were involved together in three cases, and the mitral and aortic valves were involved together in one case.

Tables 2 and 3 summarize the clinical and pathological findings in these 16 cases with neurological complications. Postmortem examination of the brain was done in all of the 11 fatal cases. Five patients had changes in sensorium (from "mildly confused" to "obtunded"), meningismus and pleocytosis (from 5 to 313 cells), but no focal neurological signs. In all of the three fatal cases in this nonfocal group, cerebral microabscesses were noted on postmortem examination. There was an associated silent frontal infarct in one of these cases, and a mycotic aneurysm and septic emboli in a second. The two surviving patients in the nonfocal group had a similar clinical presentation with headache, dulled mentation, nuchal rigidity, pleocytosis of 9 and 37 cells, and sterile spinal fluid. In one of these cases, a small left frontal and occipital blood-brain-barrier defect was found on an initial brain scan. In the other patient, there was a diffusely slow electroencephalogram (EEG) and a normal, early brain scan.

In nine patients there were focal hemispheric signs with or without sensorial changes. The deficits included hemiplegia in six patients, an iso-

lated visual field defect in one, a fluent aphasia in one and mild nondominant parietal lobe signs in one. The cause of the focal findings was an infarct in six patients, a ruptured mycotic aneurysm in one and an abscess in one. In this last patient there were diffuse signs of meningoencephalitis including a pleocytosis of 14 cells for one week before a right hemiplegia developed. In all the other patients of this group, there was a rather abrupt onset of the neurological deficit.

Two patients presented with sensorial changes and rapidly developing brain stem signs of transtentorial herniation without known antecedent hemispheric signs. On postmortem examination, multiple cerebral emboli and edema were noted in one and a ruptured mycotic aneurysm with intraventricular bleeding in the other. Endocarditis was not diagnosed before death in either of these patients.

There were four cases of mycotic aneurysms. The associated organisms included Serratia marcescens, viridans Streptococcus and Staphylococcus aureus (two cases). In two of these patients there was an angiographically verified extracranial mycotic aneurysm on the celiac trunk and the descending aorta. A massive subarachnoid hemorrhage occurred in two of the four patients. One of these patients survived with only a subtle neurological deficit. In the other two patients, unruptured mycotic aneurysms were seen at autopsy.

Diffuse microabscesses were seen in four postmortem examinations. Serratia marcescens was the causative organism in three cases and Staphylococcus aureus in one case. There were associated infarcts or mycotic aneurysm in all but one of these cases. Only one large abscess was seen in all of the patients. In this case, Staphylococcus aureus infection was present with associated cerebral infarct and unruptured cerebral mycotic aneurysm.

One pathologically studied case was unusual because of the presence of cotton fibrils in the right atrial wall. In this patient there was a viridans Streptococcus infection of the mitral and aortic valves. Foreign body giant cells were present in the right atrium, the aortic valve leaflet and the left cerebral hemisphere adjacent to a large hemorrhagic infarct.

Reports of Cases

In three cases, patients with endocarditis presented predominantly with neurological symptoms and signs. One patient was confined to a state psychiatric hospital because of confusion and paranoid hallucinations. Findings in later examinations showed an aortic murmur, fluent aphasia and mild right hemiparesis. Blood cultures grew a candida organism. The spinal fluid contained 12 leukocytes. An EEG showed a left-sided low amplitude slow wave focus. The brain scan was normal. After an aortic valve replacement, the infection was controlled with administration of amphotericin. The neurological deficit remained unchanged without further elucidation, and the patient was lost to follow-up.

A second patient was brought to the emergency room following an automobile accident. There were no signs of head injury. However, during the next three hours, the sensorium changed from lethargy to coma, and a left hemiparesis and a right third nerve palsy appeared. Emergency burr holes revealed a blue-black brain on the right and subarachnoid but no subdural blood. An arteriogram was then obtained which showed an aneurysmal dilatation of the proximal right middle cerebral artery. Later an alpha-hemolytic streptococcal organism was cultured from the blood. The patient was successfully treated with decadron, mannitol and antibiotics. Another arteriogram made several weeks later failed to show the aneurysm. Months after the insult, the only deficit was mild spasticity on the left. Although a cerebral contusion was initially suspected, the arteriogram and subsequent course suggest that a ruptured mycotic aneurysm produced this neurological situation.

A third patient presenting with neurological symptoms and signs was brought to the emergency room in a semicomatose state, became decerebrate and deeply comatose in twelve hours, and finally herniated despite therapy with osmotic agents. The scanty available history indicated that fever and malaise had been present for two weeks and headache and confusion for 12 hours. On the initial examination a mitral murmur and depressed sensorium were noted, but no focal neurological signs. The spinal fluid contained 313 leukocytes (90 percent neutrophils), 495 red cells, protein of 108 mg per 100 ml and glucose of 44 mg per 100 ml. Cerebral arteriography showed multiple blocked vessels. After death, the blood cultures grew a microaerophilic streptococcus, but the spinal fluid culture was sterile. On postmortem examination, multiple emboli were noted without evidence of mycotic aneurysm or abscess formation.

Comment

Frequency of Neurological Complications

In discussing the frequency of neurological and other complications of endocarditis in addicts, left-sided and right-sided endocarditis should be considered separately. Sole right-sided infection has been reported in 9 percent[4] to 72 percent[6] of series of endocarditis in addicts. Tricuspid infection accounted for about a third of the patients in the present study. Pulmonary embolism is the hallmark of tricuspid endocarditis;[1,2] peripheral embolic signs appear less frequently than in left-sided endocarditis[6,7] and the mortality is some two to five times less.[1,2,6] With the present data in a combined series of 165 patients,[1,2,6,7] it would appear that addicts with right-sided infections tend to be younger than those with left-sided infections (29.7 ± 0.88 compared with 36.2 ± 1.28). Moreover, in only five of 93 cases of tricuspid endocarditis from a combined series was there an infection with an organism other than Staphylococcus aureus.[2,6,7]

Neurological complications occur only occasionally in isolated right-sided infections. Ramsey and co-workers noted only one case in 28 addicts with tricuspid endocarditis reported in the literature before 1970.[2] One of 15 cases reviewed was noted in the present series.

If one considers only left-sided endocarditis in addicts, the chances of major neurological complications are greater than the 12 percent[10] to 29 percent[8] of nonaddicts with endocarditis. In Louria's review of earlier case reports, there were cerebral emboli in 45 percent of 20 published cases in which sufficient clinical information was given.[1] The present study reports a complication rate of 58 percent. The mortality of 69 percent in these patients is close to the mortality of 63 percent reported by Jones in nonaddicts with endocarditis having major neurological complication (excluding the miscellaneous complications of headache, mononeuritis and convulsions).[8]

The higher complication rate in addicts may in part be secondary to the failure of some to undergo a full antibiotic course. Follow-up medical care is often neglected, and many addicts resume their drug habit. Two and three separate bouts of endocarditis were seen in three addicts in this series.

Probably more important in determining the complication rate is the heightened virulence of the organisms seen in the addict population. The five cases of Serratia marcescens endocarditis in the present series were all associated with neurological sequelae and were all fatal. Fungal endocarditis accounted for 17 percent of the cases reviewed here. Although an identical percentage was noted in an earlier review,[14] most recent series report a much lower incidence.[2,5,6] Twenty percent of the patients in the present series were infected with a Group D streptococcal organism. In recent surveys, only six cases of enterococcus were present in a total of 123 cases of endocarditis.[1,2,4-7] Combining these six cases with the nine in the present series, the neurological complication rate was only one case in the 15 despite a mortality of 40 percent in these patients. More data clearly must be gathered before it can be determined if the embolic potential of enterococcal endocarditis is less than that of Gram-negative, Staphylococcus aureus or fungal endocarditis.

The case in which cotton fibrils were present in the heart raises the question whether foreign bodies introduced by venipuncture can affect the course of endocarditis in addicts. Foreign body granulomata unassociated with endocarditis have been reported in the lung,[11,12] liver,[13] and the spleen and kidney.[14] Surgical placement of foreign bodies in the heart apparently increases the risk of endocarditis.[15-18] One could speculate that in unusual cases, talc or cotton fibril contamination could make endocarditis more likely to occur, the infection more resistant to treatment or the embolization potential of the lesion greater.

Types of Neuropathological Lesions

With the possible exception of a delayed endarteritis,[19] all the neuropathological complications of endocarditis appear to result from either septic or nonseptic emboli. Critical factors that may determine whether a septic embolus results in a simple infarct, a mycotic aneurysm or an abscess include the site in which the embolus lodges, the virulence of the organism and the defenses of the host (including the adequacy of antibacterial therapy). The associations of abscess and infarcts in three cases and abscess, infarcts and mycotic aneurysm in two cases show that different pathological processes may be simultaneously present.

The most common neuropathological complication in this and other series of endocarditis[8,9] is embolic infarction without abscess or aneurysmal

formation. In 29 percent of the left-sided infections such simple infarcts, either single or multiple, were present. This can be compared with 12 percent in Jones' series of 385 nonaddict patients with endocarditis.[8]

Mycotic aneurysms were shown angiographically or pathologically in a fourth of those cases with neurological sequelae. This corresponds to 13 percent of the cases of left-sided endocarditis, a slightly higher incidence than the 2 to 9 percent from Ziment's review.[9]

Katz and associates have recently shown angiographically the development of a mycotic aneurysm in an endocarditis patient with a clinical infarct.[20] In this case, a segmental vascular occlusion by a septic embolus apparently resulted in an initial infarct and delayed aneurysmal formation. If arteriography would be used more frequently in this situation, the incidence of recognized aneurysms would probably be greater than the 2 to 9 percent reported. The patients in the present series in whom a mycotic aneurysm was diagnosed before death presented with an abrupt subarachnoid hemorrhage without a history of a preceding infarct. Presumably in this type of patient, the septic embolus involves primarily the vasa vasorum; or because of collateral flow, there is no clinical infarct despite a segmental vascular occlusion by the septic embolus.

Although organisms of low virulence are said to be most often associated with mycotic aneurysms,[9] Serratia marcescens and Staphylococcus aureus were isolated in three of the four cases reported here. Two additional cases of mycotic aneurysm in addicts also recently reported virulent organisms.[21] In both of these cases and in two of the cases reported here (Staphylococcus aureus and a viridans Streptococcus infection), there was an abrupt hemorrhage when the patient either was receiving no therapy or therapy with an antibiotic that was later shown to be ineffective *in vitro* against the organism. These cases tend to lend clinical support to the hypothesis discussed by Molinari and co-workers.[22] In their experimental model of mycotic aneurysms in dogs, bleeding tended to occur when no antibiotics were given; whereas, with antibiotic therapy, the aneurysms were unruptured and abscesses were seen.

The four cases of microabscesses reported here were in patients with virulent organisms who were treated from 12 days (Staphylococcus aureus) to more than a month (three cases of Serratia marcescens). Two of these four cases had associated unruptured mycotic aneurysm. The 13 percent incidence of abscesses in this series is high compared with that in most series of even acute endocarditis in the antibiotic era.[9]

Clinical Features

The main neurological diagnostic difficulty in endocarditis is the patient who presents not with focal signs but with an alteration in sensorium, often with signs of meningeal irritation. Recent reviews have emphasized the relatively common and serious nature of such "toxic psychosis" or "toxic confusional state."[8,9]

Including only those cases in which there were objective laboratory or clinical signs of neurological abnormality, 19 percent of the patients with left-sided endocarditis qualified as having primarily a toxic encephalopathy. This corresponds to a third of those patients with neurological complications. Underlying "silent" infarcts, abscesses and mycotic aneurysms were shown to be present in those cases that came to postmortem examination. Jones reports an overall incidence of "toxic psychosis" of 7 percent or about a third of those with major neurological complications.[8] The mortality of 64 percent reported by Jones is similar to the 66 percent mortality found in the present series. The mortality in the addict endocarditis patients with neurological complications is essentially the same in the group with focal signs and in those who have "toxic psychosis" without focal features.

These clinical features may be especially difficult to recognize in an addict because of the high frequency of infections in addicts, the problem of drug withdrawal, a baseline personality disorder in some, and a secretiveness and suspicion shown by many of these patients when they are isolated in medical surroundings.

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Medical
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Preimplantational Ectogenesis

Science and Speculation Concerning *In Vitro* Fertilization and Related Procedures

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*In recent years, technical advances have made preimplantational ectogenesis (*in vitro *maturation, fertilization and early embryonic development) more than a theoretical concept. Such procedures hold great promise in medical research. However, despite our newly-acquired skills in tissue culture and microsurgical manipulation, and contrary to many sensational articles in the lay press, it is not likely that preimplantational ectogenesis will soon attain wide clinical use in humans. Adverse societal attitudes, based largely upon moral and ethical dilemmas, will probably combine with still-unresolved technical difficulties to restrict the clinical applications.*

PREIMPLANTATIONAL ECTOGENESIS is a concept charged with emotion. It has stimulated both hopes and fears, and the quantity of hysterical commentary spawned by it has been colossal. On the one hand we are told that if we truly love children, we will pray for "glass wombs"[1]; alternatively, this type of work has been described as representing "unethical experiments on the unborn."[2]

In reality, however, preimplantational ectogenesis is likely to neither save nor destroy civilization as we know it. Furthermore, its immediacy of application on anything resembling a wide scale is nowhere as near as many of its proponents and antagonists alike would have us believe. The field is very much in its infancy, but as it matures it is likely to present ever-increasing opportunities in both medical research and clinical practice. Associated with these opportunities will be numerous moral and ethical dilemmas, many of them entirely novel.

In this article, we will consider the present status and possible future applications of preimplantational ectogenesis, a broad term that may be defined as the development of a germ cell or an embryo outside the body of its mother during the time before it would normally implant in the uterus. For convenience, we will divide the discussion of ectogenesis in human and nonhuman species into three stages: culture of the unfertil-

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ABBREVIATIONS USED IN TEXT

DMSO = dimethysulfoxide
DNA = deoxyribonucleic acid
FSH = follicle stimulating hormone
HCG = human chorionic gonadotropin
HMG = human menopausal gonadotropin
LH = luteinizing hormone
PMS = pregnant mare serum
PEP = phosphoenolpyruvate
PKU = phenylketonuria
PVP = polyvinylpyrrolidone

ized oocyte, *in vitro* fertilization and culture of the early embryo. It must be kept in mind, however, that these divisions are arbitrary and artificial; in reality, all of development is a continuum.

Oocyte Culture

Normal Oocyte Maturation and Its Relation to Ovulation

In female mammals, endogenous gonadotropins are secreted in a cyclic pattern, and repetitively bring a number of oocytes to the preovulatory condition. Basically, this involves an increase in the size of the oocytes, proliferation of the surrounding follicle cells and approximation of the follicular surface to the ovarian capsule. Then, at about the time of the midcycle surge of luteinizing hormone, two events take place: oocyte maturation and ovulation.[3]

To understand maturation, it must be recalled that in all known mammalian species, oogonia are transformed into oocytes only during a female's own fetal life or in the immediate newborn period; no new oocytes appear at any later time.[4,5] Each oocyte attains a follicle-cell investment, replicates its deoxyribonucleic acid (DNA) and enters prophase of the first meiotic division.[6] At this stage, the oocytes arrest, with their chromosomes drawn out long and threadlike.[7] They remain in this condition until they have undergone their preovulatory growth; then, just before ovulation, meiosis resumes. The chromosomes condense, complete the first meiotic division (with formation of the first polar body), and proceed as far as metaphase of the second meiotic division. Here, a second physiological arrest occurs. In most species, this is the point at which fertilization takes place, only after which does the second meiotic division proceed to completion. *Maturation* is the term given to the portion of meiosis between the two normal, physiological arrest points. It can be triggered not only by endogenous gonadotropins but also by exogenous hormones—usually injections of pregnant mare serum (PMS) and human chorionic gonadotropin (HCG).[3]

In most species, maturation occurs just before ovulation. The majority of mouse eggs are released from the ovary at second meiotic metaphase, although some of the earlier eggs to be ovulated are at earlier stages in meiosis, and complete maturation in the fallopian tube.[3] The maturation-ovulation relationship is quite constant for any given species. In mice, maturation begins two hours after the administration of HCG, and is completed by 14 hours, the time at which ovulation occurs. In humans, the onset of maturation takes place about 25 hours after HCG; by 36 to 43 hours, when ovulation occurs, maturation is complete. Depending upon the species, the interval between the onset of maturation and ovulation ranges from 10 to 24 hours.[3]

There are few mammalian exceptions to this maturation-ovulation relational sequence. In dogs, foxes and perhaps horses, ovulation precedes maturation; the latter presumably takes place in the tube.[3] The Madagascan insectivore Ericulus is even more unusual: after intraovarian maturation, sperm enter the ovary and fertilize the egg, only after which is the new embryo ovulated.[3]

A small number of matured, nonovulated oocytes can be found in the ovaries of most mammals.[3] This may represent the first step in oocyte atresia. In addition, maturation without ovulation may result from administration or release of smaller-than-usual quantities of HCG or luteinizing hormone (LH)—which would imply that less gonadotropin is necessary to initiate maturation than to cause ovulation.[8]

In Vitro *Oocyte Maturation in Nonhuman Species*

In vitro culture of unfertilized oocytes is possible because physical removal of an ovum from its follicle will also result in the initiation of maturation. In 1935 Pincus and Enzmann obtained rabbit oocytes from large ovarian follicles, and cultured the ova on plasma clots. Over the several hours of culture, many of the ova were observed to have extruded first polar bodies.[8] Two years

later Moricard and De Fonbrune similarly cultured mouse oocytes.[9]

Therefore, it became apparent that ovarian oocytes from large follicles could be carried through maturation if they were maintained in appropriate culture media under controlled environmental conditions. However, very little progress was made for a quarter of a century after Pincus and Enzmann's report. For one thing, there was great difficulty in obtaining satisfactory chromosome preparations for study from the matured eggs; this problem was not resolved until the late 1950's, with the tremendous breakthroughs in the technology of chromosomal preparation. The other drawback was the vagarious nature of the natural substances being used as culture media. Since the composition and toxicity of different batches of plasma and serum varied tremendously, consequently so did the rates of maturation.

A major step forward was the demonstration by W. K. Whitten in 1956 that eight-cell mouse embryos would undergo apparently normal development in a defined Krebs-Ringer balanced salt solution containing bicarbonate as a buffer, protein and a carbohydrate energy source.[10] By 1963 R. L. Brinster had redefined the medium so that it would support the development of two-cell mouse embryos.[11]

It was not a great jump from the culture of early embryos to that of prefertilization oocytes. The major early worker in this area was the English biologist R. G. Edwards. Between 1960 and 1965 Edwards published studies of the *in vitro* maturation of oocytes of several species, including rats, hamsters, pigs, cows, sheep, mice, monkeys and humans.[12-14] He tried several media, but used primarily the complex Medium 199, supplemented with 15 percent bovine serum, and antibiotics. During his experiments, Edwards was able to determine that the time sequence of *in vitro* maturation, as it is *in vivo,* is relatively constant and specific for any given species, but that there is considerable variation among species.[13]

By the mid-1960's, microbiochemical techniques had evolved to the point where J. D. Biggers, D. G. Whittingham and R. P. Donahue were able to study and report on the pattern of energy metabolism in the mouse oocyte.[15] Using the simple basic salt solution developed by Brinster, they were able to determine that for the oocyte, the optimal energy source was pyruvate; in fact, the only other compound tested that would serve at all satisfactorily in this capacity was oxaloacetate. Consequently (as we shall see) the oocyte is even more fastidious in its requirements than the two-cell embryo, which itself is more exacting than the eight-cell embryo. The authors concluded that the pattern of energy metabolism is determined in the oocyte before fertilization, and is very specific.

Biggers and his group also noticed that when the oocyte culture system included follicle cells, the energy-source requirements were not quite as specific; for example, glucose and phosphoenolpyruvate could then also support maturation.[15] This suggested that follicle cells may normally help to supply critical energy sources to the oocyte during the maturational period. This concept was followed up by Donahue, in work done with S. Stern. These investigators reported that in a culture system including follicle cells and using glucose as the sole energy source, not only would mouse oocytes mature but the follicle cells could indeed be shown to be producing pyruvate in amounts sufficient to support oocyte maturation.[16] Therefore the scientists concluded that *in vivo* either the stimulus to ovulation permitted follicle cells to initiate production of pyruvate so that maturation could begin, or it modified the oocyte in some fashion so as to permit it to react to the pyruvate being produced all along by the follicle cells.

Building upon the work of Brinster and of Biggers and associates, Donahue was able to carry out an hour-by-hour analysis of the maturation of the mouse oocyte *in vitro.*[17] In doing so, he correlated the progressive stages of meiotic chromosomal development with the culture interval after liberation of the oocyte from the follicle. By 11 hours, a significant number of ova had reached second meiotic metaphase; the peak number of 88 percent of all cultured oocytes did not reach this stage, however, until 17 hours of culture. Of the remaining 12 percent of oocytes, about half failed to initiate maturation, and half progressed only to first meiotic metaphase. No specific explanation has been offered to account for the failure of some cultured oocytes to complete maturation.

In succeeding years, the oocyte of the mouse has continued to be the favorite of developmental biologists, although attention has also been paid to the ova of rabbits,[18] guinea pigs,[19] domesticated farm mammals[20-22] and nonhuman primates.[23] Basically, the culture technique described by Brinster and adapted by Donahue has remained

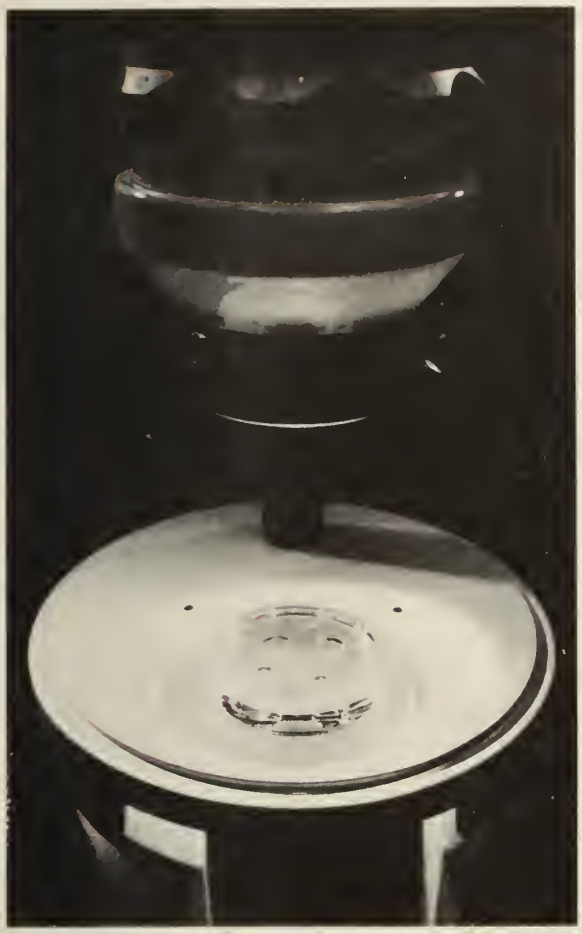

Figure 1.—Culture system for oocytes or embryos. Microdroplets of culture medium under paraffin oil, in plastic tissue-culture dish. The dish rests upon the stage of a dissecting microscope. (Photo by Jim Cummins.)

the standard.[17] Culture medium is maintained at a pH of approximately 7.2 by the use of a carbon dioxide/bicarbonate buffer system. Droplets of about 75 microliters' volume are placed at the bottom of plastic tissue-culture dishes, under a layer of sterilized paraffin or silicone oil (Figure 1). The major purpose of the oil is to act as a physical buffer, protecting against evaporation of the medium, or sudden changes in temperature or pH. The dishes are placed either in controlled gas-flow incubators or sealed desiccators, usually in an atmosphere of 5 percent carbon dioxide/95 percent air, and at a temperature of 37°C (close to normal body temperature for both mice and men). Many types of culture medium and several different atmospheric gas combinations have been utilized with this system. Although major modifications of the system have been tried,[24,25] the great majority of the work has been done utilizing the basic described technique. (The course of mouse oocyte maturation and fertilization *in vitro* is shown in Figure 2.)

Are oocytes matured *in vitro* normal and comparable to ova which have matured *in vivo?* Several measurements suggest that the two groups may be identical in many but perhaps not all respects.

For one thing, in all examined species the time interval spent in maturation appears to be about the same whether the ova mature *in vivo* or *in vitro.*[13,17] For example, Donahue found that natural maturation is complete in mice by the time of ovulation, 14 hours after the administration of HCG. This stands in comparison with the maximum of 17 hours needed for *in vitro* maturation in this species. In addition, ultrastructural studies of mouse oocytes matured either *in vivo* or *in vitro* showed no significant differences between the two groups.[26,27]

The ultimate test of normality of maturation probably is the degree to which eggs can be fertilized and subsequently develop into normal young. Oocytes matured *in vitro* generally have not been as capable of being fertilized as those matured *in vivo.* In mice, Cross and Brinster showed that the rate of fertilization *in vitro* was twice as high when ova were used that had been matured *in vivo* rather than *in vitro.*[28] It is uncertain whether the lessened capacity for fertilization shown by oocytes matured *in vitro* would be associated with offspring having greater numbers of birth defects, but there is no evidence to suggest that this would be so. Of particular interest in this respect would be a controlled study of the incidence of chromosomal abnormalities in oocytes matured *in vivo* and *in vitro.*

In Vitro *Oocyte Maturation in Humans*

The first report of human oocyte maturation *in vitro* is that of Pincus and Saunders in 1939.[29] Using human serum as the culture medium, these workers noted formation of polar bodies in 19 percent of their experimental ova, after culture periods of up to 72 hours.

There were no further reports of successful attempts at culturing human oocytes until 1965, when R. G. Edwards reported recovery from large ovarian follicles of 250 oocytes, 133 of which were examined after varying intervals of culture in Medium 199 with 15 percent fetal calf

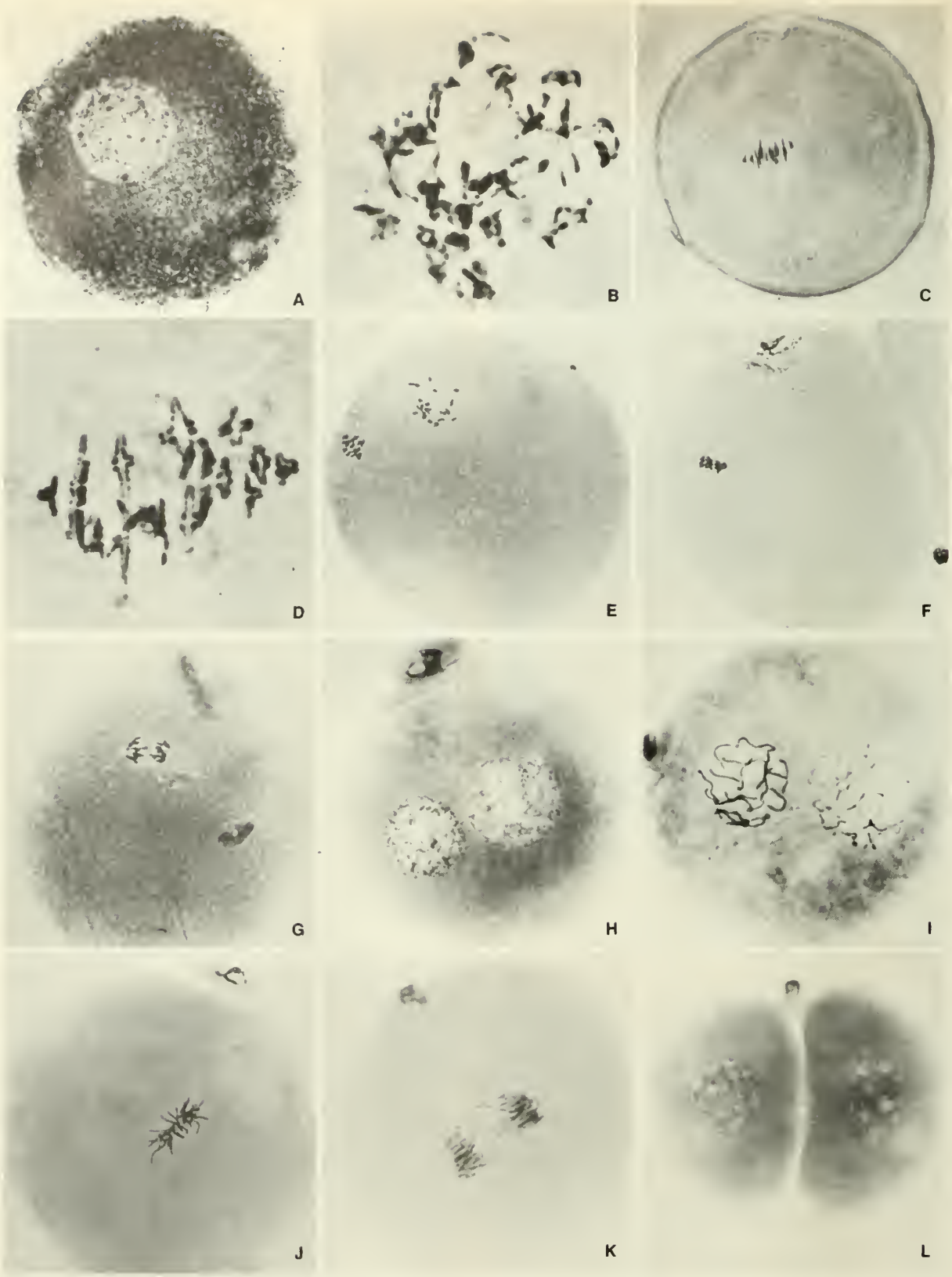

Figure 2.—The course of mouse oocyte maturation and fertilization *in vitro*. (Zona pellucida dissolved by fixative.) (Reproduced by permission from Journal of Experimental Zoology: Figures A-F, 169:237-250, 1968; Figures G-L, 180:305-318, 1972; courtesy Wistar Institute Press.)

A, mouse oocyte after liberation from follicle. Nucleus (germinal vesicle) in prophase; individual chromosomes cannot be visualized.

B, formation of chromosomes within nucleus of oocyte, before meiotic spindle formation. Two hours of culture.

C, first meiotic metaphase. Nine hours of culture.

D, high-power view of chromosomes at first meiotic metaphase.

E, first meiotic division completed. Note typical disorganization of chromosomes in polar body. Approximately 11 hours of culture.

F, second meiotic metaphase. Oocyte chromosomes organized on spindle; polar body and its chromosomes (seen at 12 o'clock) already show degeneration. 17 hours of culture. Arrest at this point pending fertilization.

G, sperm head has entered oocyte, and is beginning to swell and transform into male pronucleus. Maternal chromosomes have been activated, and are in the process of completing the second meiotic division.

H, fertilized oocyte showing (large) male and (small) female pronuclei. Second polar body is seen, with degenerating chromatin. (First polar body has since degenerated.)

I, chromosomes beginning to condense and appear in pronuclei, preparatory to first mitotic (somatic, cleavage) metaphase.

J, first mitotic metaphase, representing first actual physical contact of maternal and paternal hereditary material.

K, separation at anaphase of chromosomes, as one-cell embryo divides into two cells.

L, two-cell mouse embryo. Second polar body visible at 12 o'clock.

serum.[14] In this study Edwards was able to outline the temporal sequence of maturation for human oocytes, much as Donahue was later to do (with greater precision) for mice. He found that maturation was initiated approximately 25 hours after the onset of culture, that first meiotic metaphase occurred between 28 and 35 hours, and that second metaphase was reached between 36 and 43 hours. He commented on the prevalence of abnormal arrest at the onset of maturation and at first metaphase (though he referred to the latter as "anaphase block").

Although Jagiello, Karnicki and Ryan cultured 73 percent of 30 human oocytes to second metaphase, the ova were obtained at surgical operation, 24 hours after HCG had been given.[30] Therefore the impetus to initiate maturation had come *in vivo.*

The next report of complete *in vitro* maturation of human oocytes was that of J. F. Kennedy and R. P. Donahue, in 1969.[31] These investigators obtained 426 oocytes from surgically-excised ovaries, and attempted to culture them in media of differing complexities. They found that the rate of maturation was highest in F10 medium, intermediate in Medium 199, and lowest in the simple Krebs-Ringer salt solution with pyruvate which works so well with mouse oocytes. Altogether, only 45 percent of the oocytes reached second metaphase. It was also noted that removal of the follicle cells (cumulus) which normally adhere to the oocytes resulted in lower rates of maturation, but it could not be determined whether this was due to damage to the oocytes caused by follicle-cell removal, provision of a necessary nutrient by the follicle cells or a protective (detoxification) effect of the follicle cells.

Since 1969 other attempts have been made to culture human oocytes *in vitro,* but with no greater success than noted in earlier reports.[32,33] Human ova may be more fastidious in their culture requirements; alternatively, there may be fewer follicles of sufficient size at any one time in human ovaries than in mouse ovaries. In any case, even when human oocytes are successfully matured *in vitro,* they are, like mouse oocytes, more difficult to fertilize *in vitro* than *in vivo.*[34,35] This fact notwithstanding, results of ultrastructural studies have failed to show any morphological differences between human oocytes matured *in vivo* and *in vitro.*[36] Moreover the temporal sequence of maturation of human ova appears to be similar *in vivo* and *in vitro.*[14,37]

In Vitro Fertilization

Aspects of Natural Fertilization

Fertilization is a more complex sequence of events than is generally realized. Normally it begins with penetration of the egg by one, and only one, competent spermatozoon. This is followed by completion of meiosis in the ovum, with reduction of the chromosome number to the haploid condition; replication of DNA by both the male and the female haploid groups of chromosomes, and finally syngamy—or the union of the maternal and paternal chromosomes. This is rapidly followed by the first somatic, or cleavage, or mitotic division, which results in the formation of a two-cell embryo. (See Figure 2 for course of mouse maturation and fertilization *in vitro.*)

Most of the studies concerning the nature of the fertilization process have been done on the gametes of rabbits and laboratory rodents: the process appears to be quite similar in all species. Findings in electronmicroscopic studies[38,39] have shown that numerous spermatozoa make their way through the investing cumulus cells, presumably by release of enzymes from the region of the acrosome ("head-cap"), which is thought to be a modified lysosome. Two acrosomal enzymes have been identified: hyaluronidase and a trypsin-like acrosomal proteinase. In most species, only one sperm usually manages to penetrate the mucoprotein zona pellucida, which surrounds the oocyte proper. This zonal penetration is probably also achieved through the mediation of enzymatic digestion, the sperm following a curved course through the zona, and leaving a *penetration slit.* Upon reaching the oocyte surface, the portion of the sperm membrane at the posterior aspect of the head fuses with the ovular (vitelline) membrane, and then the rostral part of the sperm head in drawn into the egg by progressive membrane fusion and phagocytosis.

Next, a nuclear envelope surrounds the chromatin in the sperm head, thus forming the *male pronucleus.* The rest of the spermatozoon eventually disintegrates. Simultaneously, the oocyte extrudes the second polar body, completes the second meiotic division, and the chromatin becomes the *female pronucleus.* In all mammals, the two pronuclei remain separate, merely approaching each other as they replicate their chromatin.[40] Thus, there is no actual fusion of maternal and paternal pronuclei until the pronuclear membranes break down, a spindle forms, and the two

groups of chromosomes come together at metaphase of the first mitotic division. Division follows rapidly, with formation of a two-cell embryo.

It appears that before normal fertilization can occur in mammalian species, certain specific preparatory changes must take place in both the egg and the sperm. Around the time of ovulation, the ovum accumulates a complement of cortical granules: small, membrane-surrounded packages of mucopolysaccharides and hydrolases.[39] These cortical granules originate in the Golgi complexes and then move peripherally to lie directly beneath the vitelline membrane. Upon entry of the fertilizing spermatozoon, the granules are extruded from the egg, releasing their contents.[41] This is referred to as the *cortical reaction*. It is believed that the enzymes from the cortical granules modify the oocyte investments in such a way that they become impervious to further sperm penetration, thereby providing a safeguard against the development of embryos with abnormal numbers of chromosomes.[39]

The prefertilization changes in the sperm are generically referred to as *capacitation*. In 1951 Chang and Austin independently noted that freshly-ejaculated or epididymal sperm were not capable of fertilizing oocytes, but that sperm which had been preincubated for a few hours in the female reproductive tract acquired fertilization competence.[42,43] Even today, the precise nature of capacitation is obscure; however, the phenomenon may be related to removal or alteration of seminal plasma components which are bound on the surface of the sperm head.[44]

The necessity for capacitation seems to have been well established in many animal species, including rats, mice, rabbits, hamsters, sheep, ferrets and cats.[44] In primates, the evidence for its necessity is less definite.[44] In addition, incubation in the female genital tract does not appear to be specifically required for successful capacitation: in different species, capacitation has been achieved *in vitro* by incubation in follicular, tubal or uterine fluid; in serum; in solutions of β-glucuronidase, and in simple chemically-defined media, and even by exposure to Sendai virus.[44]

The morphological correlate of capacitation is the so-called acrosomal reaction. First reported in 1958 by Austin and Bishop,[45] and further elaborated in 1963 by Austin,[46] this consists of dissolution of the outer membrane of the acrosome, with subsequent loss of this structure down to the inner acrosomal membrane. Therefore it can be seen that the acrosomal reaction would result in exposure of the immediate environment to hyaluronidase and acrosomal proteinase. These enzymes are thought to play a role in the dissolution of the intercellular matrix of the cumulus and the local digestion of the zona pellucida.[47] It is of interest that in rats and mice, capacitation is not necessary for fertilization of eggs which have been stripped of their cumulus cells and zonae; fresh epididymal sperm have no trouble in penetrating these naked oocytes.[48,49]

In Vitro *Fertilization of Nonhuman Species*

In 1959 Chang described *in vitro* fertilization of rabbit eggs, which was followed by the birth of normal young.[50] Since then, as summarized by Toyoda and Chang, the oocytes of mice, guinea pigs, rats, cats, pigs and humans have also been fertilized *in vitro*.[51]

The basic technology used for *in vitro* fertilization has been quite similar from report to report, and in fact does not differ significantly from the procedure employed for *in vitro* oocyte maturation. Culture medium is set up in microdroplets under oil in tissue culture dishes, or is layered under oil in a watch glass. The sperm and ova are placed into the medium, which is then incubated for between 4 and 24 hours, usually at 37°C and in an atmosphere of either 5 percent carbon dioxide/95 percent air or 5 percent carbon dioxide/5 percent oxygen/90 percent nitrogen. Most reports have mentioned that the optimal pH is somewhat higher than that for oocyte maturation, about 7.6 to 7.8.[52] However, in mice, Iwamatsu and Chang found that pH 6 to 7 gave the best results.[53]

Criteria for successful fertilization *in vitro* have become stringent with the passage of time. The only absolute measures of success, of course, are the demonstration of a Y chromosome in the embryo, or birth of male offspring after transfer to a recipient uterus. However, the following morphologic parameters are frequently accepted as constituting evidence of fertilization: visualization of the second polar body, a sperm head in the process of transforming into a male pronucleus, and a degenerating sperm mid-piece and tail in the cytoplasm; or observation of the polar body and the fully-formed characteristic male and female pronuclei. (In some species, the male pronucleus is larger than the female.[54]) Although some workers have also accepted apparently-normal cleavage divisions as proof of fertilization,

others disagree because of the possibility that this may represent either degenerative fragmentation or the initial stages of parthenogenetic development—a process known to occur after many types of experimental manipulations of oocytes.[55,56]

A recent ultrastructural study showed that fertilization of mouse eggs *in vitro* produces embryos highly comparable to those resulting from natural fertilization.[57] The culture medium was a Krebs-Ringer bicarbonate solution, modified from Whittingham's formula. At all stages during and after fertilization, the zygotes had very similar morphology. Only minor differences could be seen, and these could not be called abnormal. The actual event of sperm penetration appeared identical *in vivo* and *in vitro*. Furthermore, the timing of the pronuclear changes, syngamy and the first mitotic division was identical to that described by Donahue after natural fertilization.[54]

On the other hand, rates of fertilization are lower *in vitro* than *in vivo*. Although higher rates have been reported,[58] usually, no more than 50 percent of oocytes become fertilized *in vitro*. This may reflect either suboptimal selection of oocytes or the fact that the ideal conditions for *in vitro* fertilization have yet to be discovered. It does not necessarily imply abnormality in the fertilized ova.

Another point of difference between fertilization *in vivo* and *in vitro* was discovered by Niwa and Chang, working with rat gametes.[59] In contrast to earlier work by Blaudau and Odor and by Austin, which showed that at the time of *in vivo* fertilization there are approximately 10 sperm in the tube for each ovulated egg, Niwa and Chang needed 3,000 to 6,000 sperm per egg to effect optimal fertilization *in vitro*. No clear reason could be put forth for this large concentration difference, which probably holds generally true for other species as well; different workers studying different species have determined the most satisfactory concentration of spermatozoa for *in vitro* fertilization to be between about 10^5 and 10^6 cells per ml of culture medium.

Although detailed investigations have not been made of the incidence of congenital anomalies in offspring after *in vitro* fertilization and transfer of embryos to foster mothers, most reports have not mentioned any increase over the rates seen after fertilization *in vivo*. An exception was the paper by Toyoda and Chang.[51] These workers fertilized rat ova in a simple defined medium and obtained 88 percent success. In the embryos which were then transferred and developed to term, there was a 50 percent incidence of microphthalmia, sometimes involving only one eye per animal. No other anomalies were seen and the peculiar cluster could not be explained.

In Vitro *Fertilization of Human Oocytes*

The first attempt to fertilize human ova *in vitro* was made by Menkin and Rock.[60] They recovered 800 eggs from ovarian follicles and tried to mature them in cultures of human serum. After approximately 24 hours, 138 of these oocytes were exposed to freshly-ejaculated human sperm in a simple salt solution, over a one- to two-hour period. Then the ova were placed back in serum. Three ova were considered by the authors to have undergone apparently normal cleavage over the 40 to 46 hours following fertilization. However, degenerative fragmentation and rudimentary parthenogenesis were not ruled out.

In 1966 Edwards and his associates tried to fertilize human oocytes that had been matured in Medium 199 with 15 percent inactivated fetal calf serum.[34] They attempted to capacitate the sperm by both *in vivo* and *in vitro* modalities: placing the sperm in rabbit uteri and tubes, recovering sperm in cervical mucus after intercourse or culturing sperm samples with small pieces of human fallopian tube. In addition the sperm were washed twice to remove seminal plasma. After 36 to 40 hours of maturational culture, the eggs were exposed to the sperm for 8½ to 42 hours, and then examined. Fertilization could not be confirmed, however, in any of the 104 exposed oocytes. In addition, 20 more oocytes were inseminated in the reproductive tracts of rabbits, and 67 in monkeys. Very few of these eggs could be recovered and none were fertilized.

By 1969 Edwards was working with a new group of investigators.[35] They used a modified Tyrode solution for capacitation, and matured the oocytes in follicular fluid alone or in combination with Hanks', Brinster's or Bavister's medium. Fertilization was carried out in Bavister's medium, and success was inferred by the finding of pronuclei and sperm midpieces, and extrusion of second polar bodies. Despite meticulous monitoring of culture components, pH and other environmental factors, only 34 of 56 cultured oocytes matured. Then, after insemination, only seven were found to have pronuclei. Even worse, some of the pronuclei were abnormal. Furthermore, five percent of control oocytes underwent

cleavage-like parthenogenetic development. The authors voiced concern regarding the poor maturation rate and possible abnormality of eggs matured totally *in vitro,* and changed their experimental course to the attempted fertilization *in vitro* of oocytes matured *in vivo.*

As a means of obtaining matured oocytes for fertilization, Edwards joined forces with Patrick Steptoe, a gynecologist skilled in laparoscopy.[37] To time ovulation, women were given injections of human menopausal gonadotropin (HMG) and HCG; the optimal schedule was determined to be three injections of 225 IU HMG between days 2 and 9 of the menstrual cycle, and a single dose of 5,000 IU HCG between the 9th and 11th day. A group of 46 infertility patients served as subjects. Steptoe carried out laparoscopy between 29 and 31 hours after HCG administration, based upon Edwards' previously-cited data on oocyte maturation. Using an aspiration device of original design, Steptoe eventually was able to recover approximately one preovulatory oocyte per ovary. Best results came from follicles with diameters between 1 and 2 cm.

The oocytes recovered by Steptoe, which were mostly at or near first meiotic metaphase, were incubated for one to four hours in a mixture of follicular fluid and the fertilization medium being tested: Whittingham's or modifications of Waymouth's, Ham's F10 or Bavister's media, all at pH 7.5 to 7.6.[61] Next, both sperm and eggs were washed with fresh fertilization medium, and then they were incubated together for 12 to 15 hours. At this point, the embryos were transferred to medium which had been designed to support cleavage: Whittingham's, Whitten's, Waymouth's, 199 or Ham's F10—all modified to some degree and all adjusted to pH 7.3. Criteria for fertilization included the observation of two pronuclei, two polar bodies and a sperm tail in stained preparations; two pronuclei in the live egg, or morphologically-normal cleavage of the zygote, preferably after having observed pronuclei.

The number of embryos transferred from the fertilization to the cleavage medium was not mentioned, but 38 embryos were reported to have cleaved in culture up to the 16-cell stage, and one or more embryos were produced from 29 of 49 patients undergoing laparoscopy. Fertilization was achieved in all media tried except Ham's F10; however, this medium, with 20 percent inactivated fetal calf serum, seemed optimal for support of the cleavage embryos, when the osmolality was raised from the conventional 287 mOsm per kg to 300 to 305 mOsm per kg. Based on his observations, Edwards offered the hypothesis that the follicle cells of the cumulus might themselves effect sperm capacitation through the production of progesterone, a hormone capable of destabilizing lysosomal membranes such as are found in the acrosome.

Luigi Mastroianni's group has also been active in this area. Seitz and co-workers cultured 16 human ova in F10 medium, and inseminated them with human sperm that had been washed and then incubated in a monkey uterus.[62] Six ova were considered to have been fertilized and to have cleaved to stages from two to eight cells.

In 1973, Soupart and Morgenstern reported on the attempted maturation and fertilization *in vitro* of 44 human oocytes.[63] The maturation culture was composed of one part Bavister's medium and three parts follicular fluid; the fertilization medium was Bavister's adjusted to pH 7.6. The addition of follicle-stimulating hormone (FSH), LH and HCG to the fertilization medium appeared to increase the incidence of sperm penetration into and through the zona pellucida. This was interpreted as a capacitation effect, apparently supporting Edwards' hypothesis, in that the action of the gonadotropins might have been expressed via mediation of follicular-cell hormone production. Overall, however, only one oocyte appeared to have been fertilized.

After having used Edwards' and Steptoe's techniques for *in vitro* fertilization, an Australian team of physicians reported having transferred a human zygote at the 6- to 8-cell stage. However, menstruation occurred nine days after transfer.[64]

It is still impossible to comment on the normality of human oocytes fertilized *in vitro.* To this point, the applied criteria for fertilization have all been only presumptive, and very few oocytes have fulfilled them. No Y chromosomes have been identified in early human cleavage embryos, and although fertilization most likely did occur when ova were found to have two pronuclei, two polar bodies and a degenerating sperm mid-piece and/or tail, this still does not absolutely rule out parthenogenesis—especially in view of Edwards' finding of five percent spontaneous parthenogenetic development of control oocytes,[34] and the fact that parthenogenesis can be induced in the mouse by hyaluronidase. Furthermore, no embryos have progressed far enough (that is, beyond implantation) to observe anomalies of bio-

chemical or structural development. And in the absence of karyotypes of these embryos, we cannot rule on their chromosomal normality or abnormality. Soupart and Strong reported on the comparative ultrastructural features of a human tubal pronuclear egg, and oocytes fertilized *in vitro*.[65] They found no basic ultrastructural differences, but did notice some vacuolization of the cultured zygotes, suggestive of degeneration and therefore also suggesting that at least their own technique of ovum culture was not yet ideal.

Embryo Culture

Postfertilization Culture of Nonhuman Embryos

As reviewed by Biggers and Stern,[66] the first recorded attempt to culture mammalian embryos was that of Brachet, who in 1912 and 1913 maintained five-day rabbit embryos on plasma clots. Lewis and Gregory in 1929 also tried to culture rabbit embryos in plasma. In 1930 Gregory Pincus succeeded in supporting cleavage of rabbit embryos in several culture media, and in 1934 Pincus and E. V. Enzmann carried out the first transfer of cultured embryos into the uteri of recipient does, obtaining live, healthy offspring.

However, as we mentioned during the discussion of oocyte maturation, it was primarily the work of W. K. Whitten, R. L. Brinster and J. D. Biggers and his group that really opened up the field of embryo culture in particular, and preimplantational ectogenesis in general. Whitten and Brinster showed that cleavage could be obtained in simple defined media. Then, these investigators and others proceeded to use this information to investigate the metabolic requirements of mammalian embryos at different stages of cleavage. The acquisition of such knowledge led in turn to the development of more satisfactory and reproducible methods of culture.[67]

By far the greatest amount of work in postfertilization embryo culture has been done on mice, and rabbits are all alone in second place. Interest has also been shown in other small laboratory mammals and, because of the potential applicability to practical animal husbandry, in sheep and cows.

Brinster's 1963 paper is still the classic in the field.[11] In it, Brinster described the technically-simple method of embryo culture in microdroplets of medium under paraffin oil in a tissue-culture dish. The medium was a simple Krebs-Ringer salt solution, with bicarbonate as a buffer, bovine serum albumin as a protein source and stabilizing agent, sodium lactate as the energy source and antibiotics to guard against contamination. By the use of this system, Brinster was able to culture two-cell mouse embryos, obtained from the fallopian tubes, all the way to preimplantation blastocysts. Furthermore, he determined that the rate of development was highly reproducible and closely paralleled that *in vivo*.

Brinster followed up his initial work with several publications in which he manipulated his culture conditions in order to determine various optima, as evaluated by the number of two-cell embryos which would cleave to blastocysts. The best osmolarity was found to be 276 mOsm per kg, and the most satisfactory pH 6.82—this in spite of the facts that rat and rabbit tubal fluids are alkaline and that all of Brinster's work where pH was not a variable was carried out at pH 7.38.[68]

Brinster's experiments indicated that a fixed-nitrogen source was necessary for cleavage; bovine serum albumin at a concentration of 1 mg per ml seem optimal.[69] The albumin could also be replaced by equivalent quantities of the constituent amino acids. When this was done, however, a nonprotein polymer such as polyvinylpyrrolidone (PVP), acacia, dextran or Ficoll had to be added; otherwise, the embryos tended to float to the surface of the droplets. Omission of single amino acids was well tolerated, with the sole exception of cystine. In opposition to Brinster's data, however, Cholewa and Whitten were able to obtain cleavage of two-cell mouse embryos in the absence of a fixed-nitrogen source.[70]

Studies of energy requirements of the cleaving mouse embryo have showed a general trend toward less restrictive needs with increasing development. As previously mentioned, the unfertilized oocyte will undergo maturation only when supplied with either pyruvate or oxaloacetate. This great selectivity holds true for the first cleavage division as well, only pyruvate or oxaloacetate being able to serve as energy sources for the pronuclear zygote.[15] (However, lactate or phosphoenolpyruvate [PEP] will prevent degeneration of embryos for up to 48 hours of culture, and if pyruvate is added after 24 hours of culture in lactate, the embryos will then complete the first cleavage division.[71]) By the time the ovum has reached the late two-cell stage, lactate and phosphoenolpyruvate will function fully as sources of energy to support cleavage of the 2-cell embryos to the blastocyst stage.[72] In fact, a combination of

pyruvate and lactate may give the best rates of cleavage.[73] By the eight-cell stage, as had originally been reported by Whitten, glucose can support further development; in fact, cleavage will take place in the presence of *either* glucose *or* albumin.[74] This progressive change in energy requirements suggests corresponding developmental changes in the embryo during the preimplantational period. There may occur alterations in cell permeability to different compounds. In addition, changes occur in the activities of several enzymes, as summarized by Biggers and Stern.[66]

Even oxygen concentration in the culture atmosphere has come under scrutiny. Auerbach and Brinster determined that two-cell mouse embryos will proceed normally to blastocysts as long as the oxygen concentration is at least 1 percent.[75]

Again, the issue of normality arises. With regard to cultured mouse embryos, this question has been examined primarily on a functional basis.

Bowman and McLaren determined that *in vivo,* mouse embryos between the two-cell and the blastocyst stages had a cell doubling time of ten hours. In the early stages of culture, this rate was identical, but subsequently fell off to about 24 hours.[76] In addition it was determined that only 20 to 30 percent of cultured mouse embryos resulted in live fetuses at 17 days after transfer of blastocysts, compared with 50 percent success when the blastocysts were taken from the uterus.[77] There was an excess of both preimplantational and postimplantational mortality, and the surviving fetuses from the cultured embryos were about 100 mg lighter than the controls. Furthermore, there seemed to be an inverse relationship between the duration of culture and the viability and weight of the fetuses. Menke and McLaren also discovered that blastocysts maintained *in vitro* had a lower metabolic rate than those taken from the uterus.[78]

The first report of total *in vitro* preimplantational development leading to the birth of live young was that of A. B. Mukherjee in 1972.[79] Oocyte maturation, sperm capacitation, fertilization and cleavage to the blastocyst stage were all carried out *in vitro.* Previously, the nearest anyone had come to achieving successful total preimplantational ectogenesis was described by the report of Cross and Brinster, who matured mouse oocytes *in vitro,* and fertilized them *in vitro* with sperm capacitated *in vivo.*[28] After transfer, live fetuses were found upon autopsy of the recipients at 15 days' gestation.

Mukherjee matured mouse oocytes in Ham's F10 or in modified Whitten-Biggers Medium. Sperm were obtained from the epididymis, and capacitated by four hours' incubation in a 1:2 mixture of heat-inactivated follicular fluid and human tubal fluid. Fertilization was carried out by exposure of oocytes for 24 hours to capacitated sperm cells in Ham's F10 medium under paraffin oil. The embryos were then cultured for three days in fresh medium. At this point the blastocysts were transferred into the uteri of mice made pseudopregnant by mating three days previously with vasectomized males. Transfer was achieved by puncturing the utero-tubal junction with a micropipet, and blowing in the embryos. To be certain that any liveborn young had indeed originated from the ectogenetic embryos, the sperm and oocytes were taken from a strain of mouse with a coat color different from that of the recipient females and the vasectomized males to which they had been mated.

Not only is Mukherjee's report the first of its kind, it is also to date the only one. Furthermore, consideration should be given to the low rate of success he obtained. Of 325 oocytes placed into maturation culture, 195 showed formation of the first polar body, 140 were placed into fertilization medium, 32 two-cell embryos resulted and 11 blastocysts were recovered for transfer. Eventually, five liveborn, apparently normal, progeny were obtained—an ultimate yield of only about 1½ percent of the ovarian oocytes initially placed into culture.

Rabbit embryos have received less attention than those of mice. Ogawa and co-workers, using a highly complex medium, were able to culture 58 of 67 one-cell embryos to the eight-cell, morula or blastocyst stages.[80] Kane obtained an 81 percent yield of blastocysts from one-cell embryos cultured in a medium devoid of any carbohydrate energy source; it could not be discerned whether the embryos were using endogenous energy sources or the amino acids present in the medium.[81] Brackett and associates used ova and sperm matured and capacitated *in vivo,* carried out *in vitro* fertilization and obtained apparently normal cleavage in 43.7 percent of 302 oocytes.[82] In all, 22.6 percent of 31 transferred cleaved ova developed to term birth in genetically-dissimilar recipients.

Van Blerkom and co-workers employed ultrastructural and microbiochemical techniques to compare preimplantational rabbit embryos which

had cleaved *in vivo* and *in vitro*. No differences were seen using an electron microscope during the first five days of embryogenesis.[83] Then, a combination of electrophoresis and radioautography showed that qualitative patterns of protein synthesis *in vitro* paralleled those *in vivo*, stage by stage.[84]

Tervit and co-workers recovered sheep and cattle embryos from the tube at the one-cell to the eight-cell stages and cultured them in a medium based upon the composition of sheep oviductal fluid.[85] After three to six days in culture, some of the embryos were transferred to recipients. In the sheep, a small number of viable embryos were found at slaughter of the recipients on day 13 or 14 of pregnancy. One of the recipient cows was found to be pregnant, as diagnosed by rectal palpation on day 35. This animal went to term, but no mention was made of the offspring.

A concept which has received much popular attention is that of the freezing of embryos. In 1971, Whittingham recovered mouse embryos at either the eight-cell or the blastocyst stage, and froze them at −79°C for 30 minutes in phosphate-buffered saline with 15 percent polyvinylpyrrolidone, an agent which protected the embryos against rupture.[86] After thawing, 75 percent of the eight-cell embryos appeared normal and 52 percent developed into blastocysts after 48 hours of culture. After thawing and a subsequent 24 hours of culture, 62 percent of the frozen blastocysts were considered normal. Of 19 transferred eight-cell embryos, 21 percent developed into normal offspring, as did 69 percent of 13 transferred blastocysts.

A year later, Whittingham extended his work.[87] He froze more than 2,500 mouse embryos, from the one-cell to the blastocyst stage, for up to eight days, at either −196° or −269°C. Dimethylsulfoxide (DMSO) or glycerol was added as a protective agent, and freezing and thawing were both done at very slow rates. Depending upon the original stage when frozen, from 50 to 70 percent of the embryos developed into normal preimplantation blastocysts when thawed and cultured in Whittingham's medium. Approximately 1,000 of the survivors were transferred to virgin recipients, 65 percent of which became pregnant —a rate equal to that achieved after natural insemination of virgin mice. In the mice which did conceive, 43 percent of the transferred embryos developed into apparently normal term fetuses or live young.

In further experiments, Whittingham and Whitten were able to freeze embryos for up to eight months, transfer them by air from Bar Harbor, Maine, to Cambridge, Massachusetts, and obtain live births after transfer to recipients.[88]

Less work of this sort has been done with larger animals. Moore and Bilton recovered sheep embryos at the one- to four-cell stages, and as morulae.[89] These embryos were cooled to 5°C for ten minutes to six hours, after which they were cultured for 48 hours. Approximately 70 percent of the rewarmed embryos progressed normally in culture. Furthermore, of 30 cooled-and-warmed embryos that reached the blastocyst stage, and were then transferred to recipient ewes, 11 developed into liveborn lambs.

Human Embryo Culture

Some of the work done to date in human embryo culture has been described previously, in connection with *in vitro* fertilization. An additional report by Steptoe, Edwards and Purdy that is worthy of note appeared in *Nature* in 1971.[90] There, they described the extended preimplantational culture of six human embryos, utilizing already-described techniques of fertilization and cleavage culture. Two embryos developed only to the morula stage; they were found to have 23 and 30 cells. Two other embryos formed blastocele cavities, but the entire embryos appeared abnormal, and in fact were found to contain only 16 and 20 cells. The last two embryos developed into apparently normal blastocysts. One was examined at 159 hours of culture, and was found to have 110 nuclei. The other blastocyst was treated at 147 hours so that its cells might be karyotyped. It was found to have 112 cells, but no chromosomal spreads were suitable for karyotyping. The authors estimated that the cells probably were diploid.

The team of Seitz, Rocha, Brackett and Mastroianni matured 50 follicular oocytes for 24 hours at F10 medium, with 20 percent heated human female serum, and 25 micrograms of sodium estrone sulfate per ml.[62] Sperm were capacitated in the uterus of a midcycle rhesus monkey. After fertilization, the embryos were transferred to fresh medium identical to that used for maturation. Of the 50 original ova, 8 apparently underwent cleavage, reaching stages between 2 and 12 cells. No cleavage was seen among 20

control oocytes which had been incubated with either washed, ejaculated sperm or sperm-free washings from a monkey uterus. Therefore, it was concluded that capacitation is indeed necessary in humans. Cited by the authors as evidence of fertilization were: sperm in and around the zona pellucida, visualization of two polar bodies, observation of "chromatin" in some of the blastomeres, progressive cleavage stages and failure of the controls to cleave.

Implications of Preimplantational Ectogenesis

Both in scientific journals and the lay press, preimplantational ectogenesis has been the subject of considerable discussion and controversy. Some of this has been sober, but a good deal more has been ill-founded in scientific fact, emotional and even hysterical. Preimplantational ectogenesis deals intimately with basic questions of human life and human reproduction, which forces anyone who would consider the issues to think through his basic concepts of right and wrong, usually a very painful process.

Preimplantational Ectogenesis in Clinical Medicine

The most frequently-discussed application, and in fact the expressed goal of Edwards' and Steptoe's work, is the relief of infertility caused by obstruction of the fallopian tubes. A very large number of women suffer from this problem, and so would be candidates for laparoscopic recovery of oocytes, *in vitro* fertilization with the sperm of the husband and subsequent reimplantation into the wife's uterus.

Two of the leaders of the opposition to this procedure are theologian Paul Ramsey and biologist-ethicist Leon Kass. Referring to *in vitro* fertilization as "unethical experimentation on the unborn,"[2] Kass argues that on ethical grounds such work cannot be justified. First, he says, the risk cannot be determined without carrying out the procedure on humans, and second the prospective fetus is incapable of giving informed consent.

Part of the opposing argument to Kass' position has been presented by ethicist Marc Lappé.[91] Lappé argues that the small amount of animal data available do not suggest that the risk of *in vitro* fertilization is large. Nor might one really expect it to be, after manipulation of these embryos which have not yet reached the period of organogenesis. Lappé also reminds us that no official effort has been made to prohibit reproduction by two carriers of autosomal recessive diseases like phenylketonuria (PKU) or sickle cell anemia, where the 25 percent risk of affected offspring would almost certainly exceed any risk associated with *in vitro* fertilization. This argument could be extended to point out that 3 to 5 percent of all newborn infants resulting from *in vivo* fertilization suffer from some kind of birth defect and that children conceived by this technique do not give informed consent. If prospective parents can give consent for *in vivo* fertilization, it is difficult to understand why it could not be given for the *in vitro* procedure as well.

However, Lappé does point out that with the present dearth of reliable safety data, it might be a good idea to accumulate more information in animal experiments, before recommending that this work be done in humans. If findings from extensive animal experimentation—including primate work—are reassuring, then preimplantational ectogenesis might be offered, with appropriate explanation, to individual infertile couples. This manner of procedure would not be different from any other developing medical undertaking.

What of the possible psychological effects of human *in vitro* preimplantational development? It is quite certain that the first offspring to be produced in this manner will attain celebrity status. However, this does not appear to be a fatal disease. In addition, one might wonder whether parents would relate in a healthy fashion to such children. We know of no evidence to suggest the contrary.

The question may arise as to the disposal of "extra" ova and embryos. Suppose four eggs should be obtained from the ovaries of an infertile woman, and they all become fertilized and develop into preimplantational blastocysts. Logically, all these embryos should belong to the donating couple, whose prerogative it would be to determine their fate. The couple might decide that all the embryos must be given the opportunity to implant, that any extras might be given to a woman desirous of pregnancy but with no ovaries of her own, that they might be used for research or that they should be washed down the sink.

A clinical application closely allied to the relief of tubal infertility is the relief of ovarian infertility. In this circumstance, a woman, induced by love or money, would donate an ovum to be fertilized *in vitro* by the sperm of a man whose wife lacked ovaries but had a normal uterus. The

resulting embryo would then be transferred to the uterus of this woman, who would carry the fetus to birth. Such a procedure should be no more objectionable than artificial insemination.

A more controversial variation involves the issue of surrogate uteri, or, as it has been termed, "rent-a-wombs." Here, the oocyte would be fertilized by the sperm of the husband of the egg donor, and the embryo would then be transferred to the uterus of another woman whose menstrual cycle had been properly timed. This woman might receive a fee to carry the pregnancy to term. Presumably, the donor of the oocyte would not want to bear the pregnancy because of health reasons, job obligations, fear or vanity. Much has been made of the possibility of "exploitation of the poor" by such a scheme. However, the other side of the coin is represented by a few women who have called our office (though we are not engaged in work of this nature) to inquire whether they might volunteer their services should such ventures become reality. They state that they love being pregnant, and would arrange to always be in this condition if it were not for the matter of having to keep the babies. They think that hiring out their uteri would be a fine way to make a living. On reflection, it seems inconsistent to categorically deny such women this kind of livelihood, while we permit and even encourage people to earn money by such dangerous means as coal mining, or racing little cars around a track at 200 miles per hour. Perhaps the genuine major concern in the application of this scheme is the possibility that the woman attached to the rented womb might become psychologically attached to her tenant, and not wish to relinquish possession at birth. Or, conversely, that should the baby be born abnormal, the "donor parents" might refuse to accept the child.

Another possible application of preimplantational ectogenesis relates to the work of Gardner and Edwards, who were able to accurately determine the sex of preimplantation rabbit embryos by determining the sex chromatin in biopsied fragments of the trophoblastic portions.[92] Should this work prove possible in human embryos, it would provide an alternative for determination of sex of offspring. Such preimplantational sex determination would be highly preferable to the only method of sex choice now available: amniocentesis with abortion of embryos of the undesired sex. The technique would be welcomed by couples for use in routine family planning, as well as by women and men who carry the genes for X-linked disorders like hemophilia and Duchenne muscular dystrophy.

At some time in the future this technique of embryo biopsy might be extended considerably. Karyotyping of the cells would provide a method of screening for chromosomal diseases, such as Down's syndrome. Autosomal recessive disorders which manifest as inborn errors of metabolism secondary to enzyme deficiencies might be detected by microchemical assays. Perhaps even multifactorially-caused birth defects such as neural tube defects or cleft lip and palate may eventually be found to be associated with a characteristic biochemical abnormality in the preimplantation embryo. Therefore, one day, *in vitro* fertilization and embryo culture could become the preferred mode of reproduction, with transfer to the uterus of only genetically-healthy embryos. In this way, considerable inroads could be made in the prevention of many all-to-common serious birth defects.

Propositions of this sort invariably elicit cries of "Brave New World," and fears of governmental control of reproduction, complete with compulsory "elimination of the unfit."[93] This, however, could only happen if a government were to obtain the power to regulate reproduction in the first place. Reproductive control would necessarily be the result, not the cause, of slavery. And if a government ever should be able to wield such power, it is likely that reproductive control will be the least of our worries. Far more likely to become reality is the concern that the more militant members of Right-to-Life groups will succeed in legislating *their* brand of morality, thereby forbidding individual couples to elect these particular reproductive techniques.

Eventually, manipulation of preimplantational embryos might also be used in genetic engineering, to permit replacement of a defective gene by a normal one. This could be done by exposure of the embryo to a virus containing the properly-functioning gene needed by the embryo: the virus would integrate itself into the chromosomes of the embryo, becoming, in fact, a basic part of the genotype of the new organism.[94] Alternatively, the problem might be solved by injection of a number of cells from a genetically-competent embryo into the blastocele cavity of the deficient embryo. In this fashion, a chimera would be formed.[95]

In summary, the foundations of civilization

probably would not tremble if the gametes of some men and women were to make union in plastic tubes rather than in fallopian tubes. But before this becomes an accepted practice, it would seem preferable, as suggested by Lappé, to gather considerably more animal data, in order to better determine the safety factor. Just how significant and representative were Chang's microphthalmic rabbits?

In any event, it seems premature to recommend the use of preimplantational ectogenesis in humans. Aside from the issue of safety, the technology simply is not sufficiently mature. Edwards' two published photographs of blastocysts appeared normal, and so have the photographically-reproduced embryos cultured by some other groups of scientists. But still, we have no definitive evidence that *in vitro* fertilization in humans has yet been accomplished. No Y chromosomes have been identified in these embryos. Moreover, there still has been no published report providing the details of last year's sensational verbal claim by D. C. A. Bevis that he had produced three children in 36 trials of *in vitro* fertilization and transfer.[96] Perhaps the best evidence that preimplantational ectogenesis is not likely to become routine in humans in the near future is provided by the work of Mukherjee in mice. In this species, where oocytes are plentiful, easily obtained and easily transferred in a sterile manner, only between one and two oocytes in every 100 were able to complete total preimplantational ectogenetic development, and then develop to term after transfer. This is probably just as well: in the time it will take to improve the technology and determine the safety of preimplantational ectogenesis, society will have the opportunity to slowly assimilate the concept and adjust its attitudes with regard to it.

Preimplantational Ectogenesis in Medical Research

Even if no human beings ever result from preimplantational ectogenesis, the procedures still hold considerable potential for amelioration of human problems via basic research.[97-100] The most obvious set of applications in this regard would center around investigations of peri-fertilization events. Many important aspects of chromosomal behavior at this crucial time would be amenable to investigation: for example, normal and abnormal chromosomal disjunction, chiasma frequencies and mechanisms of terminalization, and the behavior during meiosis and cleavage of both balanced and unbalanced translocations. Study of gametes and early embryos might provide clues important to the solving of hitherto-unexplained cases of habitual abortion and infertility. On the other hand, a better understanding of fertilization, including the cortical reaction and capacitation, might lead to the development of more effective and safer contraceptives. Investigations concerned with the activation of new enzyme systems in the developing embryo would be important to our knowledge of control of gene activity during development; closely related to this concept would be studies of the inactivation of the X chromosome in female embryos, and investigations having to do with cellular differentiation and dedifferentiation, so important in cancer research. The concept of keeping embryos in the deep-freeze would be (and in fact is) of great fascination to both conservationists interested in new ways of safeguarding the survival of endangered species, and commercial animal breeders interested in new ways of increasing profits.

Conclusion

Preimplantational ectogenesis offers considerable potential for improving the human condition. However, the field is in its infancy, and too much should be neither expected nor attempted too soon. A properly slow and critical approach should both guard against unfortunate results and give society the opportunity to adjust and reshape some basic philosophical concepts.

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Specialty Conference

Moderator
LESLIE J. SCHOENFIELD, MD, PhD

Discussants
LEONARD I. GOLDSTEIN, MD
JOEL PANISH, MD
J. MANNY SHORE, MD

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Gallstones

Cholesterol saturation of bile has a primary role in the pathogenesis of gallstone formation. Predisposing factors should be considered. The characteristic features of biliary colic are important to keep in mind, as well as the fact that a history of fatty food intolerance is not of value in the diagnosis of gallstones. The technique of endoscopic retrograde cholangiography is useful for the diagnosis of bile duct stones in jaundiced patients and in patients with a strong clinical history, but in whom findings on oral and intravenous cholangiograms are within normal limits. Improved techniques of operative cholangiography to diminish the incidence of retained gallstones have been developed. Also, choledochoscopy provides a remarkable technique for diagnosis and choledocholithotomy. The dissolution of gallstones with chenodeoxycholic acid is an experimental procedure. This bile acid is thought to act by increasing the chenodeoxycholic acid pool size and decreasing cholesterol synthesis and secretion, thereby reversing the defects responsible for gallstone formation.

LESLIE J. SCHOENFIELD, MD, PH D:* The purpose of this conference is to discuss recent advances in the pathogenesis, diagnosis and management of gallstones. Dr. Leonard Goldstein will review the mechanism of gallstone formation, risk factors for the development of gallstones and selected clinical features. Dr. Joel Panish will describe the diagnostic and therapeutic use of endoscopic retrograde cholangiography. Dr. J. Manny Shore will discuss advances in operative cholangiography for the prevention of retained gallstones, as well as advances in choledochoscopy for the operative diagnosis of ductal stones and choledocholithotomy. Finally, I will present the current status of the efficacy, adverse effects and mechanism of action of chenodeoxycholic acid in the medical dissolution of gallstones.

CLINICAL ASPECTS OF GALLSTONE DISEASE

LEONARD I. GOLDSTEIN, MD:† The occurrence of gallstones, Ingelfinger noted a few years ago, has not been an "in disease" and has been "grossly neglected by the medical profession."[1] This situation is now changing; research advances in the pathogenesis of cholesterol gallstones have brought us to the threshold of a new era, promising both prophylaxis and medical treatment. The need for such therapy is emphasized by the prevalence of gall-

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stones in the United States. Keeping in mind the "iceberg phenomenon" of asymptomatic stones, gallstones occur in approximately 16 to 20 million Americans (10 percent of men and 20 percent of women in the 55 to 64 age group). They develop in about 1 million people each year. In more than a third of a million persons annually, cholecystectomy is carried out, with 8,000 patients dying from complications of cholelithiasis and the operation each year. In women, cholecystectomy is a more common operation than appendectomy.[2] The cost of cholecystectomy and related problems is more than a billion dollars each year.

Types of Gallstones

The pathogenesis of gallstones and the potential for their dissolution by medical means depends on the type of gallstone. Mixed cholesterol stones account for about 80 percent of all stones analyzed in the United States.[3] These contain at least 70 percent cholesterol and, in addition, bile pigment, bile acids, calcium salts and a protein matrix. Such stones (seldom larger than 2 cm) may be either multiple, round or faceted as a result of pressure of adjacent stones. If these stones contain enough calcium, they may be radiopaque. Pigment stones (less than 10 percent of all stones) are composed of bile pigment, calcium and a matrix of organic material. These calculi are usually multiple, small, dark-colored, irregular, hard and glistening; about 10 percent are radiopaque. Pigment stones are found in patients with chronic hemolysis,[4] in Orientals with parasitic infections and in patients having biliary obstruction and infection, especially with Escherichia coli.[5] In this review, we shall concentrate on cholesterol gallstones, their pathogenesis and clinical associations.

States of Cholesterol Gallstone Formation

Cholesterol gallstone formation may be divided into three stages: saturation, crystallization and growth.[6]

- *Saturation*

This critical stage involves alteration of the biliary lipid proportions, resulting in an abnormal bile saturated with cholesterol. Bile that is saturated or contains excess cholesterol relative to the other biliary lipids is prerequisite to gallstone formation and has been termed lithogenic.[7,8] Supersaturated bile is thermodynamically unstable

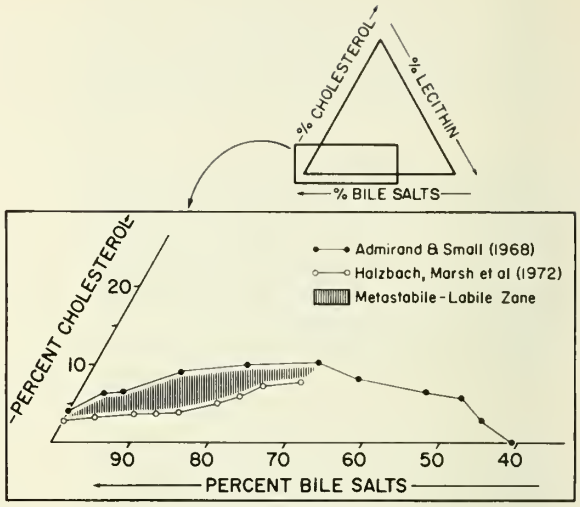

Figure 1.—Biliary lipid composition of bile expressed on triangular coordinates. Points below the metastable-labile zone indicate unsaturated bile. The zone defines supersaturated bile as metastable when nucleation of cholesterol is slow (lower limit of zone), and labile when it is rapid (upper limit). Above the zone, cholesterol is in a crystalline or liquid crystalline phase. (Courtesy of Dr. Martin D. Carey.)

and may precipitate. It has the potential for, but does not always result in, gallstone formation.[9-11]

Saturated bile may be produced in the liver, or normal hepatic bile may become saturated in the gallbladder. Current evidence supports the conclusion that the liver is the source of this abnormal bile.[7,8] Cholesterol gallstone formation could therefore be considered a primary hepatic disease. Alternatively, an abnormality of the enterohepatic circulation could induce the liver to secrete saturated bile.[12]

How does the liver produce saturated bile? Normally, cholesterol is insoluble in water but is brought into solution in bile by its molecular association with bile acids and phospholipids. The predominant phospholipid in bile is lecithin. The water-soluble bile acids act as solvents for lecithin and cholesterol in bile, and can incorporate cholesterol-lecithin liquid crystals into molecular aggregates called mixed micelles.[13] These mixed micelles have a finite capacity to dissolve cholesterol. Therefore, the solubility of cholesterol in bile depends primarily on the relative proportions of bile acids, lecithin and cholesterol.

The relative molar proportions of biliary lipids may be plotted on triangular coordinates (Figure 1).[14] Any point within the triangle represents a combination of the three components, expressed in millimols and totaling 100 percent. Any point

below the line of cholesterol saturation has sufficient concentration of bile acids and lecithin to maintain cholesterol in micellar solution. Points on this line represent bile saturated with cholesterol, whereas above the line cholesterol is in a crystalline, liquid crystalline or supersaturated state. Normal bile composition lies within the micellar zone.

Additional methods for determining cholesterol solubility and modifications in the original Admirand and Small line[14] have been proposed (Figure 1).[15] Metzger and associates[16] have defined a lithogenic index. Other workers have determined ratios of the concentration or secretion rates of cholesterol to that of bile acids plus lecithin. The most applicable method to express lithogenicity remains yet to be determined.

The liver might produce saturated bile by either a decreased secretion of the solubilizing lipids (predominantly bile acids, as bile acids stimulate synthesis and secretion of biliary lecithin)[17] or by an increased secretion of cholesterol.[18] The evidence favors a combination of these two mechanisms.

Decreased Secretion of Solubilizing Lipids—Bile Acids

In patients with gallstones[19,20] there is a significantly smaller total, cholic and chenodeoxycholic acid pool than in matched controls without stones. Biliary bile acid secretion has been reported to be decreased or normal in Caucasians with gallstones,[21] despite a decreased bile acid pool.

Why is the bile acid pool decreased in most patients with saturated bile? A defect in hepatic bile acid synthesis has been proposed as one possible explanation. Normally, bile acids are formed in the liver as the major catabolic and excretory products of cholesterol.[22] The initial and rate-limiting step in the formation of bile acids is the 7-α-hydroxylation of cholesterol.[23]

In man, the total bile acid pool is about 2 to 4 grams. Almost all of the hepatic output of bile acids is resorbed actively in the ileum and returned to the liver via the portal vein. The removal of bile acids from the portal blood is virtually complete in one passage through the liver. Inasmuch as this enterohepatic cycling occurs 6 to 8 times a day, 18 to 24 grams of bile acid are secreted daily.[24]

Hepatic bile acid synthesis is controlled by a negative feedback mechanism, whereby the rate of synthesis varies inversely with the rate of return of bile acids to the liver.[25] The enterohepatic circulation of bile acids, therefore, determines the rate of hepatic synthesis and secretion of bile acids. Bile acid synthesis is increased by interruption of the enterohepatic circulation;[26] a 20 percent interruption, however, produces saturated bile in man.[27] A diminished return of bile acids to the liver normally should stimulate hepatic bile acid synthesis. By contrast, the liver of gallstone patients may not be able to increase production in response to this decreased return of bile acids.[28] This defective bile acid synthesis has been attributed to an hepatic enzyme defect. Recently, Nicolau and colleagues[29] measured (and our group has confirmed)[30] the *in vitro* bile acid synthesis rate in the livers of patients with gallstones. Both groups found that hepatic cholesterol 7-α-hydroxylase activity was strikingly reduced. These preliminary data suggest an enzymatic basis for the reduced bile acid pool in patients with gallstones, although a direct relationship between synthesis and pool size or secretion has not been established.

The hypothesis of "inappropriate repression" has been questioned. The size of the bile acid pool and the number of enterohepatic circulations of the pool determine the total amount of bile acids secreted by the liver. Previously, it had been assumed that a low rate of bile acid secretion could be inferred from the existence of a small bile acid pool. Northfield and Hofmann,[31] however, determined that in patients with gallstones small bile acid pools were associated with normal secretion rates—a finding that suggests a high rate of recycling. They found that secretion rates remain constant over a wide range of pool sizes. Because this implies normal bile acid return to the liver, the finding of a normal synthesis rate suggests a normal feedback regulation of bile acid synthesis. Similarly, in cholecystectomized patients with complete interruption of the enterohepatic circulation, bile acid synthesis was four times that of normal or cholecystectomized subjects with an intact circulation.[28,32]

To summarize, certain data suggest that an abnormality of the enterohepatic circulation may be instrumental in inducing the liver to secrete saturated bile.

Increased Secretion of Cholesterol by the Liver

The cholesterol secretion rate in bile is increased in Caucasian women with gallstone dis-

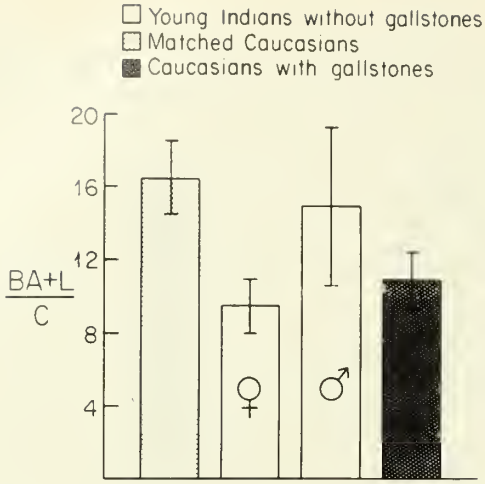

Figure 2.—Ratios (Mean ± 2 S.E.) of bile acid (BA) plus lecithin (L) to cholesterol (C) designated in the ordinate. These ratios were significantly lower among young Indian women without gallstones than among white controls and Indian men. (Reproduced with permission from *The New England Journal of Medicine.*[36])

ease. Increased cholesterol secretion can result either from excessive cholesterol input or deficient cholesterol conversion into bile acids, or both.[18] Increased hepatic synthesis of cholesterol appears to be responsible for the increased secretion of cholesterol. Nicolau and co-workers[29] found (and again, our group has confirmed)[30] an increased activity of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase, the rate-limiting enzyme for cholesterol synthesis in the liver of gallstone patients.

In summary, a dual defect, that is, an increase in cholesterol synthesis and secretion, and a reduction of bile acid synthesis and secretion, may be the basis for bile saturation. Supersaturation of bile with cholesterol is prerequisite to the precipitation of cholesterol and the subsequent formation and growth of cholesterol gallstones.

- *Crystallization*

In this stage, the excess cholesterol is precipitated from saturated bile. Bile then has two physical states: a solid phase, consisting of cholesterol crystals (or gallstones); and a liquid phase, consisting of bile saturated with cholesterol.

- *Growth*

This final stage begins with the formation of microscopic stones, perhaps by further growth of the crystals originally precipitated. The rate of stone growth is determined by the balance between the rate of precipitation and the rate of dissolution or passage of crystals into the intestinal tract. Gallstones usually grow in the gallbladder, where bile remains for several hours before being emptied into the duodenum. Biliary stasis, the frequency and efficiency of gallbladder emptying, and infection may play a role at this stage.[33]

High-Risk Groups for Cholelithiasis

Specific Populations

American Indians have a high incidence of gallbladder disease.[34] Recent studies document the magnitude of the problem in the Pima Indian population. Gallstones occur in 70 percent of Pima women by age 30, and they develop in 70 percent of Pima men in later life. Gallstones were symptomatic in about half of these subjects. A similar incidence of symptomatic stones has been found among Chippewa women in northern Minnesota.[35] In this population, the ratio of bile acid plus lecithin to cholesterol in duodenal bile in young women without gallstones was significantly lower than in a matched control group of Caucasians, and not different from that found in white women with gallstones (Figure 2).[36]

Heredity

Genealogy studies support the widespread clinical impression that there is a genetic basis for gallstone disease; familial aggregation has been reported frequently. Definite evidence of gallbladder disease was found in the mother or father of 33 of 100 patients in whom operations were carried out on the biliary tract.[37] Definitive or suggestive evidence of gallbladder disease was found in a sibling, parent or the offspring of 72 percent of these patients. Findings in a study of biliary lipid composition in siblings of young patients with gallstones showed a higher incidence of saturated bile (and therefore a greater likelihood of subsequent development of gallstones) than in a matched controlled population.[35] However, a Danish study of twins[38] showed discordance for gallstone disease in monozygotes who were 40 years of age or older, therefore excluding a simple genetic explanation. Dietary and environmental factors may influence genetic predisposition.

Ileal Disease

In patients with disease of terminal ileum or with small bowel resection there is an increased

incidence of cholesterol gallstones.[39,40] This increased incidence of cholesterol gallstones is presumably due to diminished bile acid absorption and pool size and the resultant decrease in biliary cholesterol solubilization. Dowling and colleagues[41] found that nine of ten patients with ileal disease had supersaturated bile.

Miscellaneous

In patients with coronary artery disease, peptic ulcer, vagotomy, gastric retention, cirrhosis, hyperparathyroidism and other clinical disorders[42] there may be an increased incidence of gallstone formation. The exact mechanisms of gallstone formation in these conditions are unclear and deserve further study.

Pregnancy

Gallstones are more common in women who have had children than in nulliparous women, although the degree of parity does not correlate with the prevalence of gallstones. During the progesterone phase of the menstrual cycle and during pregnancy, the humeral mechanism that usually elicits contraction of the gallbladder and relaxation of Oddi's sphincter is impaired.[43] The resultant increase in the stasis may be an important factor superimposed on changes in biliary lipid composition.[44]

Obesity

Gallstones are more common in obese patients than in thin patients or in the general population. Sarles and co-workers[45] in France have shown that patients with gallstones consume significantly more calories than control subjects. Moreover, they reported a significant direct correlation between gallstone formation in man and the concentration of cholesterol in bile, as well as the total calories ingested, regardless of the amount of fat, carbohydrate or protein in the diet.

The synthesis of cholesterol is proportional to the total body weight and, therefore, is increased in obesity. In obese patients who have gallstones, body weight correlates with biliary cholesterol.[46] Weight reduction has been shown to cause a lowering of cholesterol synthesis, and therefore it would seem likely that weight reduction would also decrease hepatic secretion of cholesterol. A recent report[47] indicated that bile composition in obese patients (during a period of weight reduction on a 1,000-calorie-per-day diet) showed a relative increase in lithogenicity in five or ten patients studied in the course of weight reduction. The lithogenicity of bile temporarily becomes worse during weight loss, but once weight is stabilized at a reduced level, bile becomes consistently less saturated.

Medications

Birth Control Pills—Estrogen-Containing Compounds

Two reports from the Boston Collaborative Drug Surveillance Program suggest that women of child-bearing age who used oral contraceptives, or postmenopausal women who had taken estrogen for menopausal symptoms, had an increased risk (2 to 2½ times that of a control group) of having gallbladder disease.[48,49] Pertsemlidis and co-workers[50] showed that patients given oral contraceptives developed an increase of cholesterol concentration in bile, and a decrease of bile acid synthesis rate and pool size. These findings show that contraceptive pills increased the saturation of bile with cholesterol.

Clofibrate

Clofibrate (Atromid-S®) is an inhibitor of cholesterol synthesis. This hypocholesterolemic agent, however, has been reported to increase cholesterol saturation of bile.[51] Furthermore, in another study clofibrate caused an increase of cholesterol concentration in bile and a decrease in the concentration, pool size and synthesis of bile acids.[50] It was not surprising, therefore, that the coronary drug project study of patients receiving long-term dosages of clofibrate found a more than twofold increase in incidence of gallstones in patients treated with clofibrate.[52]

Symptoms

In about 50 percent of patients with cholelithiasis symptoms develop secondary to biliary tract disease. The reason gallstones cause symptoms or complications in one person and not in another remains an enigma.

Two common myths or misconceptions concerning the clinical manifestations of cholelithiasis have been clarified. Fatty food intolerance or other qualitative dyspepsia, eructation, flatulence, aerophagia, pyrosis or other vague epigastric discomforts do not contribute to the diagnosis of cholelithiasis. These associated symptoms are fortuitous and comparably prevalent in about 50 percent of patients without gallstones.[53] Dyspeptic symptoms are nonspecific and not re-

lated to the presence of gallstones; the removal of the gallbladder will not consistently relieve these symptoms.

Biliary colic is the most important symptom in the diagnosis of cholelithiasis. Characteristically, the pain is of sudden onset, often severe and steady, lasting as long as three hours (usually less than one hour in 40 percent of cases). This pain does not increase and decrease in intensity and is not typically "colicky."[54] Therefore, the term biliary colic appears to be a misnomer.

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY (ERCP)

JOEL PANISH, MD:* The technique of ERCP consists of introducing a right-angled viewing fiberoptic duodenoscope into the second portion of the duodenum; visualizing the ampulla of Vater; cannulating the papilla with a small catheter and introducing radiopaque dye into the biliary tree or the pancreatic duct or both.[55-58]

Indications

- *Differential diagnosis of jaundice*—It is no longer necessary to observe a problem jaundice case for weeks in order to decide whether the cause is intrahepatic or extrahepatic. If the customary diagnostic procedures fail, we advocate ERCP early in the course of jaundice.
- *Evaluation of postcholecystectomy syndromes*—The technique is useful when there is suspicion of postoperative stricture, new or retained common bile duct stones or a long cystic duct stump; for example, in patients who have symptoms of recurrent pain, fever, abnormal findings on liver function tests without jaundice, and in patients in whom cholecystectomy has been carried out.
- *Suspected cholelithiasis*—Another use is for evaluation in the small group of patients whose clinical history suggests cholelithiasis (perhaps in whom there have been minimally abnormal findings on liver function tests) and in whom results on oral cholecystogram and intravenous cholangiogram have been normal.
- *Suspected biliary tract disease with a history of allergy to iodine*—In our experience these patients tolerate intraductal injections of dye without adverse reaction.
- *Suspected carcinoma of the pancreas.*
- *Patients with recurrent pancreatitis*—The technique may be used to evaluate for ductal stones, strictures or pseudocyst, and to help formulate the type of surgical approach most feasible for correction of cause of recurrent pancreatitis. The pathologic anatomical findings on pancreatogram help to decide in advance what type of surgical procedure would have the best chance of success in relieving the disease process.
- *Patients diagnosed as having primary biliary cirrhosis*—The technique is useful for ruling out with certainty any extrahepatic biliary block.
- *Endoscopic sphincterotomy and removal of common bile duct stones*—This procedure has been successful as reported in both the Japanese and German literature (with excellent two-year follow-ups).[59,60]

Technique

Contraindications to carrying out the examination are the presence of acute pancreatitis, a positive hepatitis B antigen and acute myocardial infarction within the preceding six weeks.

The patient is fasted overnight; a 5 percent dextrose/water solution is given intravenously in the right arm; the patient is placed in the left lateral position and premedicated to the point of drowsiness with meperidine (Demerol®) or diazepam (Valium®), or both, administered intravenously. The Olympus JF scope is introduced into the stomach and passed under direct vision through the pylorus into the second portion of the duodenum. The patient is then placed in the prone position and the ampulla of Vater is located and an "en face" view is achieved. (If duodenal hypermotility is a problem, 1 mg of glucagon is given intravenously; if it persists, intravenous administration of probanthine may be tried.) A small cannula is then introduced through the scope into the papillary orifice.

The ductal system that the examiner wishes to view is identified by injecting a small amount of 60 percent renograffin solution and observing the flow of dye on a fluoroscopic screen. The pancreatic duct is usually outlined with 2 to 10 ml of dye, under gentle pressure. The biliary tree will tolerate 20 to 50 ml of dye. If both ductal systems are not seen, further manipulation of the cannula to gain entrance into the desired duct will have to be carried out. This may entail repositioning the scope or the patient, or both. Once the desired duct is opacified, radiographs are obtained, both with the scope and cannula in place and after they

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are removed. The diagnostic accuracy of the examination depends on the clarity of the radiographs obtained and upon the radiologic equipment used.

Complications

In almost all patients, a postprocedure chemical pancreatitis will develop, with levels of serum amylase rising as high as 300 to 400 units for one

Figure 3.—Cholangiogram interpretation. **A,** normal pancreatic duct, common bile duct stone. **B,** pancreatic duct in recurrent pancreatitis. **C,** carcinoma, body of the pancreas. **D,** gallstones; normal cholecystogram.

to two days. However, in less than 1 percent does there develop clinical pancreatitis with abdominal pain or fever, or both, and these resolve within four to five days. There is a distinct possibility of infection in the presence of a pseudocyst; if a pseudocyst is shown to be present, administration of antibiotics should be started immediately and the patient observed closely. If an infection occurs and is not rapidly alleviated by medical measures, immediate surgical drainage of the pseudocyst is indicated.

The danger of ascending cholangitis developing in a patient with a high-grade extrahepatic block is a definite possibility. If such a lesion is suspected clinically, administration of prophylactic antibiotics should be begun 24 hours before the procedure; should the clinical suspicion be proved radiologically, treatment should be maintained for 48 hours thereafter. If such a lesion is encountered during the examination and the patient has not been receiving antibiotics, drug administration should be started immediately. These measures usually prevent or treat cholangitis successfully, thereby eliminating the necessity for immediate surgical intervention. If cholangitis occurs and is unresponsive to antibiotic therapy within 24 to 48 hours, immediate operation is indicated.

Results

Our current success rate in cannulating and showing the desired duct is about 85 percent; common bile duct, 75 percent, and the main pancreatic duct, 95 percent. The common bile duct is more difficult to cannulate, particularly in the presence of carcinoma of the head of the pancreas. It is possible to cannulate the papilla of Vater after gastric resection with Billroth I or II anastomoses, or in the presence of cholecystoduodenostomy, choledochoduodenostomy, sphincterotomy or sphincteroplasty. The examiner's rate of success is directly proportional to the number of procedures he has previously done.

Results of interpretation of cholangiograms have been excellent (Figure 3). Stones have been discovered in both the gallbladder and common bile duct when findings on cholecystography and intravenous cholangiography were reported as normal. Although there may be significant difficulty in filling the intrahepatic biliary radicles, by placing the patient supine and with the head down, proper filling and interpretation become possible.

The major interpretive difficulty lies in the differential diagnosis of chronic pancreatitis and carcinoma of the pancreas.[61] Similar ductal changes may be present in both diseases. It appears that this difficulty can be resolved with more experience and by utilizing magnification radiologic techniques.

It has not yet been shown whether earlier diagnosis of pancreatic carcinoma is possible, and whether the ultimate survival of the patient with this disease can be improved.

Future

The future appears promising. Electrocautery sphincterotomy with basket removal of common bile duct stones has been safely carried out. Long-term results relating to sphincter stenosis[59] and recurrent stones are not yet available, however.

Opacification of the entire pancreas by means of radiopaque dye enhanced by drugs appears possible. Pressure measurements of the sphincter of Oddi, indicating normal and pathologic effects of various drugs thereon, are being carried out and have therapeutic implications. It is now possible to collect cytological specimens directly from the pancreatic duct; this may aid in the earlier detection of cancer and perhaps influence surgical cure of that disease.

CHOLEDOCHOSCOPY

J. Manny Shore, MD:* The recent invention of the "rod-lens" optical system has led to the design of an improved rigid choledochoscope that overcomes limitations of previous biliary endoscopes (Figure 4).[62] This system allows miniaturization, so that the 5 cm exploring horizontal limb—incorporating optical, lighting and irrigating systems—measures only 5 by 3 mm in cross section. The right-angle construction and compact design eliminate difficulties encountered with previous scopes and overcome troublesome manipulation associated with flexible instruments. The wide viewing angle, increased light transmission, excellent resolution, extreme depth of field and infinity focus provide the exquisite image quality so essential for prompt endoscopic orientation. These qualities permit mastery of the endoscopic technique by surgeons after a minimum of training and experience. A standard fiberoptic light source and light transmitting cord and a saline pressure

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Figure 4.—Right-angled choledochoscope with Hopkins optical system. **a,** viewing eyepiece; **b,** attachment for light cord; **c,** attachment for irrigation; **d,** exploring horizontal limb, 5 cm long and 5 by 3 mm in cross section.

irrigation system complete the apparatus. Continuous irrigation is required to keep the ductal system distended for proper observation. The equipment is gas-sterilized.

Technique

The choledochoscope is introduced through the choledochotomy incision after completion of choledochal exploration. Technical details for assembling and properly utilizing the instrument have been described elsewhere.[63] The entire stone-bearing portion of the biliary system can be visualized, from the ampulla to the tertiary hepatic radicles (Figure 5). Abnormal changes—such as the presence of calculi, cholangitis, neoplasm, diverticula or strictures—can be promptly and accurately identified. Generally, calculi found by endoscopy can be blindly removed by manipulation after withdrawing the scope. When this is not possible, stone-retrieving instruments passed through a separate guide channel attached to the scope can be advanced under visual control. In

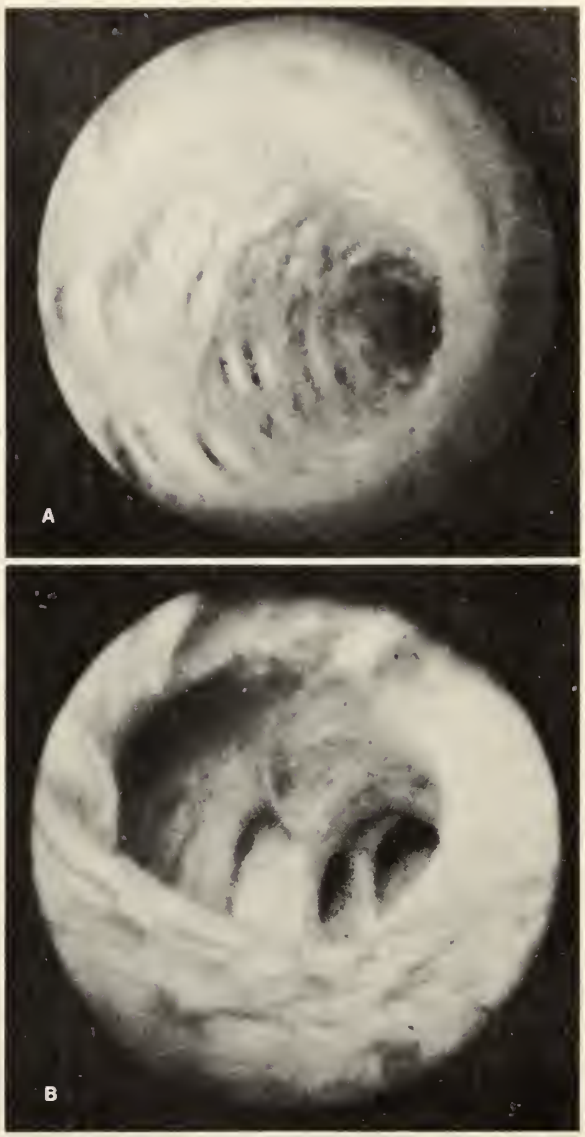

Figure 5.—Endoscopic views of biliary tract. **A,** distal common bile duct and sphincter of Oddi. **B,** hepatic ducts.

rare instances, a calculus visualized by endoscopy defies removal by all available techniques, and is managed by a biliary bypass procedure. When a neoplasm of the biliary tract is identified, it can be precisely biopsied under visual control.

Clinical Experience

A total of 342 patients have had choledochotomy, choledochoscopy and operative cholangiography carried out at the Cedars-Sinai Medical Center between 1960 and 1974 (Table 1). While our experience with the first two endoscopic instruments noted in the table was satisfactory, the vastly improved mechanical and optical qualities

of the present choledochoscope have rendered the others obsolete; superior performance now qualifies this instrument as the definitive biliary endoscope.

Between 1970 and 1974, the new choledochoscope was evaluated in 84 patients in whom primary choledochotomy was carried out and 19 patients in whom secondary exploration was done. In each case biliary endoscopy was done after choledocholithotomy with conventional instrumentation. When overlooked stones were detected, endoscopy was repeated following their removal, until clear ducts were visualized. Completion operative and postoperative T-tube cholangiograms were obtained in all patients.

Results

In 84 primary explorations for stones, no calculi were found in 30 patients. In 53 of 54 patients with calculi the ducts were cleared of all calculi by exploration, endoscopy and cholangiography. In one patient (1 percent) an overlooked stone was found by postoperative T-tube cholangiography. Calculi were also retained in two of 19 patients (10 percent) in whom secondary choledocholithotomy was done.

Biliary endoscopy was helpful to the surgeon in most of the cases, especially in the detection and removal of calculi missed by initial cholangiography and conventional instrumentation. It also facilitated operative management in complex cases by providing precise information by direct visualization. When filling defects or nonpassage of dye into the duodenum were found, biliary endoscopy clarified interpretation of completion operative cholangiograms. The overall result was one of increased efficiency, accuracy and reduction of operating time.

Discussion

While the use of completion operative cholangiography has detected many calculi missed by instrumental exploration, overlooked stones are still detected postoperatively in approximately 10 percent of choledocholithotomies.[64-69] The use of other intraoperative devices, such as the Fogarty biliary catheter[70] and the Eisman ultrasonic probe,[71] has failed to reduce the incidence of missed stones significantly beyond that of cholangiography. Operative biliary endoscopy, however, has consistently been found by investigators[63,72-82] to decrease the number of retained calculi to less than 2 percent of choledocholithotomies. Even fewer stones are overlooked, since stones that are visualized but not removable can be treated definitively by primary duct-drainage procedures. Although the latter type of stones may be retained, their detection by endoscopy has led to prompt corrective surgical procedures, thereby eliminating the probability of symptomatic recurrence.

The precise observation provided by choledochoscopy has been of value in many ways. Removal of missed calculi identified by endoscopy has been facilitated. This has occasionally been possible only under direct endoscopic guidance. The definitive information provided can promptly indicate appropriate operative strategy—for example, the decision to carry out either a transduodenal exploration or a biliary intestinal bypass procedure. The proper interpretation of doubtful or suspicious findings on cholangiograms has on several occasions shortened operating time by eliminating the need for repeat cholangiograms, reexploration or duodenotomy.

The major application of operative biliary endoscopy is in the management of choledocholithiasis. Tumors of the biliary tract can be visualized and biopsy specimens taken, but they are rare. Differentiation of distal duct obstruction due to carcinoma of the head of the pancreas or to chronic pancreatitis is usually not possible by endoscopy.

The technique of biliary endoscopy can be readily learned; the important anatomic landmarks are easily identified. Unlike endoscopic examination of other organs, there is no complex anatomy to master and any abnormalities are quickly recognized. The atraumatic nature of the choledochoscope is shown by the absence of duct

TABLE 1.—*Experience with Biliary Endoscopy, 1960-1974*

Procedure	*Wildegans Scope (Rigid)* 1960-1964	*Fiberoptic Scope (Flexible)* 1965-1970	*Berci-Shore Scope (Rigid)* 1970-1974	*Total*
Primary choledochotomy	54	160	84	298
Secondary choledochotomy	5	20	19	44
TOTAL	59	180	103	342

injury and a low incidence of postoperative complications.

With the introduction of the image amplifier and the "rod-lens" choledochoscope into the armamentarium of the biliary surgeon, a streamlined technique of choledocholithotomy has evolved. The procedure can now be condensed into an efficient stone tracking operation consisting of the following steps:

- *Initial operative cholangiography*—The use of the image amplifier for operative cholangiography eliminates most sources of diagnostic error. Localization of duct pathology before choledochotomy guides subsequent exploration. Documentation of dye passage into the duodenum before operative manipulation eliminates confusion in the interpretation of subsequent films.
- *Guided choledocholithotomy*—Guidance by the initial cholangiogram permits prompt definitive retrieval of demonstrated filling defects by the least traumatic maneuvers. Passage of a Fogarty biliary catheter distally confirms patency and may deliver residual calculi.
- *Choledochoscopy*—Safe and accurate visualization of the stone-bearing portion of the biliary tract is accomplished. Residual stones can be readily seen and retrieved. Conditions that require a concomitant biliary drainage procedure—such as nonremovable calculi or ampullary fibrosis—can be accurately identified.
- *Completion operative cholangiography*—This time-honored step may now be safely eliminated if good-quality initial cholangiograms and biliary endoscopy are routinely done.

Summary

An improved rigid choledochoscope with a "rod-lens" optical system provides rapid, safe and accurate visualization of the biliary tree. Residual stones can be readily seen and retrieved, and biopsy specimens of intraductal neoplasms can be taken under visual control.

In a recent series of 84 patients in whom primary choledochotomy, biliary endoscopy and operative cholangiography were carried out, all calculi were recovered from 53 of 54 ducts containing calculi; a retained stone was found by postoperative cholangiography in one patient (2 percent). The incidence of retained stones has been similarly lowered by all investigators incorporating biliary endoscopy in their armamentarium.

ADVANCES IN OPERATIVE CHOLANGIOGRAPHY

Any assessment of operative cholangiography should begin with a review of current practice. In approximately 60 percent of patients in whom cholecystectomy is done, there is no indication for exploration of the duct. Despite the advice of many investigators that routine cholangiography should be done in such patients,[65-69,83-87] it is frequently omitted and none of these ducts are explored. In the remaining 40 percent of patients, one or more of the indications for choledochotomy is present. In this situation most surgeons today use cholangiography selectively in an attempt to decide which ducts should be opened and which can be apparently left safely alone. When there is a relative indication for exploration and there are negative findings on the operative cholangiogram, the duct is usually not explored; this pertains to approximately 25 percent of cholecystectomies. In the other 15 percent, there is either an absolute indication (such as cholangitis, positive findings on an intravenous cholangiogram, a palpable calculus) or the operative cholangiogram gives positive findings and the duct is explored. Follow-up studies from many centers using the above approach have found that in approximately 4 percent of patients reoperation will be required for common duct stones in the future.[66,87-91] These findings are supported by the Commission on Professional and Hospital Activities. In 1970, 380,000 cholecystectomies were done in this country; during the same time, 19,000 (5 percent) reoperations on the biliary tract, mostly for retained stones, were recorded.

Closer analysis of the sources of error in operative cholangiography can pinpoint specific groups of patients in whom common duct stones are not being detected. Numerous authors* have shown that routine operative cholangiograms will show silent, unsuspected stones in approximately 4 percent of patients. These calculi are overlooked by surgeons who fail to add operative cholangiography to every cholecystectomy. False-negative findings on cholangiograms result from limitations of conventional technique, as well as from errors in interpretation and judgment. A negative finding on an initial cholangiogram in a patient with an indication for choledochotomy creates a dilemma: which one is correct? If the indications

*References 64,66,67,69,83-85,87,92-95

are strictly obeyed, the duct will be explored in far too many cases (40 percent). One of the chief advantages of cholangiography has been a decrease in the number of choledochotomies because of radiologic selection of patients with choledocholithiasis. However, when choledochotomy is circumvented by a negative finding on a cholangiogram, in the face of indications, there is a built-in risk: deliberate choledochotomy in patients under these circumstances has disclosed an error of 10 percent.[64,66,67,86] Completion operative cholangiograms also miss stones in approximately 10 percent of choledocholithotomies, as shown by postoperative T-tube cholangiograms.[64,66,70,87,96]

The overall incidence of stones missed during cholecystectomy is shown in Table 2. It is noteworthy that of approximately 6 percent failures, by far the most (5 percent) occurred in patients in whom the ducts were never opened, either because routine cholangiography was omitted or because negative results on the initial operative cholangiogram precluded choledochotomy in the face of indications. Stones retained following choledocholithotomy constitute a minority. This correlates well with the 4 percent to 5 percent incidence of retained stones that are clinically apparent postoperatively.

Recent technologic advances have afforded an opportunity to enhance the quality of operative cholangiograms and thereby increase their accuracy. The use of a thick-walled catheter that can be easily secured to the cystic duct by a Hemoclip[97] obviates the objections to routine cholangiography based on technical considerations. The incorporation of image amplification, television fluoroscopy and aimed spot films eliminates frequent errors of conventional operative cholangiography due to faulty positioning, timing and exposure. Satisfactory films can be obtained with a portable "C" arm x-ray unit available in most community hospitals. Figure 6 illustrates the more

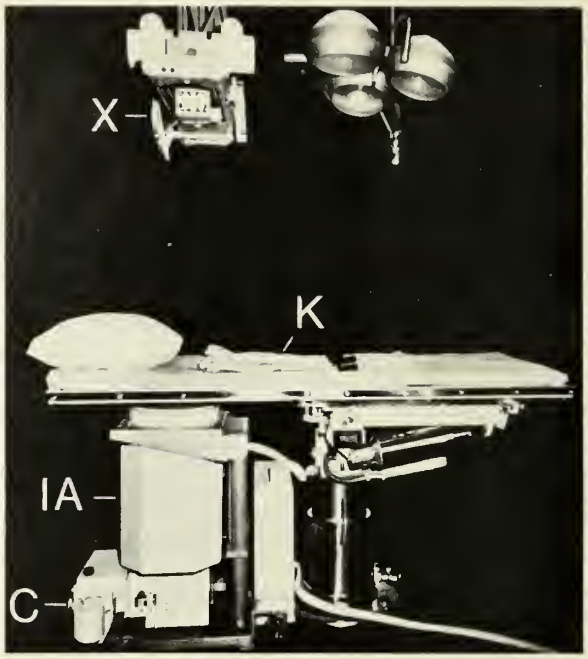

Figure 6.—Equipment for fluoroscopic operative cholangiography. K: Kifa operating table with coordinate radiolucent table top. IA: Mobile image amplifier with beam splitter, television camera and 70 by 70 mm roll film camera (C). X: Overhead x-ray tube. Television monitor is not shown.

versatile equipment currently under evaluation at Cedars-Sinai. A hydraulically controlled Kifa operating table with a radiolucent "floating" table top, permitting movement in two axes for proper positioning, is employed.[98] The ceiling-mounted x-ray tube is aligned with the mobile image amplifier beneath the table. During injection of radiopaque dye, the image is viewed fluoroscopically on a television monitor and can be relayed to a roll film camera for permanent 70 by 70 mm aimed spot films. Image magnification and video recording for instant replay and detailed observation are also available. The filling and emptying phases are observed throughout fluoroscopically, permitting proper timing and positioning of x-ray exposures. Small volume in-

TABLE 2.—*Residual Stones Following Cholecystectomy*

Clinical Group	*Percentage of Cholecystectomy*	*Residual Stones*	
		Percentage of Group	*Percentage of Cholecystectomy*
No indication for choledochotomy			
No cholangiogram, no choledochotomy	60	4	2.4
Indication for choledochotomy			
Cholangiogram negative: No choledochotomy	25	10	2.5
Cholangiogram positive: Choledochotomy	15	10	1.5
TOTAL			6.4

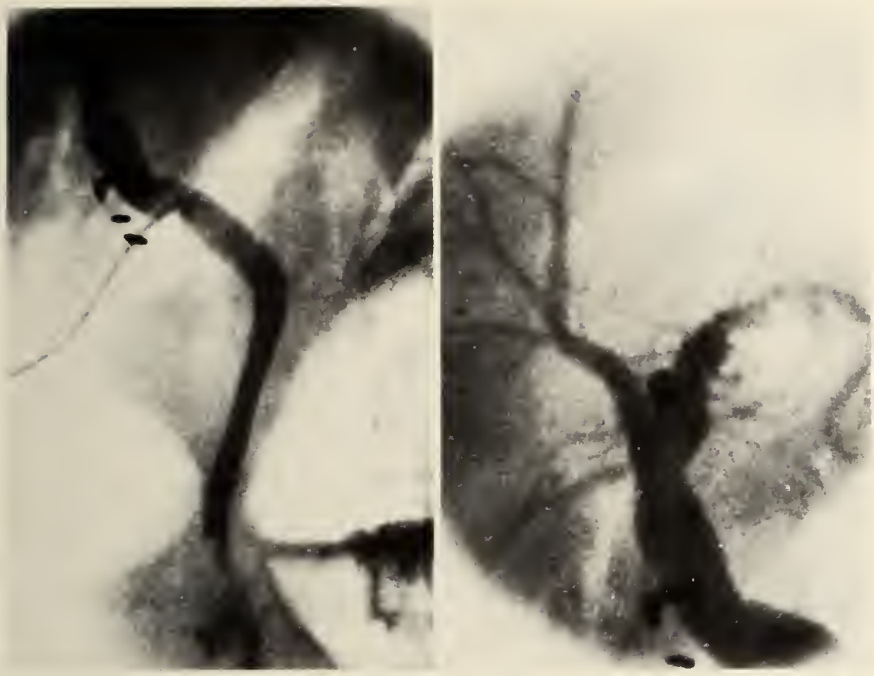

Figure 7.—"Spot" films of operative cholangiograms. **Left,** common bile duct and sphincter. **Right,** hepatic ductal system.

TABLE 3—*Advances in Operative Cholangiography*

Fluoroscopic viewing
Position control
Aimed spot films
Image magnification
Instant replay
Reduced radiation
Functional observation

crements (2 to 5 ml) of 25 percent Hypaque provide optimal visualization in most cases. Observation of rapid emptying into the duodenum signals the need for faster dye injection to fill the hepatic radicles. Proper positioning for spot film exposure of the magnified image (Figure 7) is readily obtained by moving the table top. The dynamic observation of sphincter activity may be useful in evaluating functional biliary disorders. The dry x-ray exposures are available for examination in a special magnifying viewer within minutes. The advantages of fluoroscopic operative cholangiography are summarized in Table 3.

It is anticipated that this approach will eliminate the failures of conventional techniques. Routine cholangiography will detect silent common duct stones and lead to their removal. Fluoroscopic cholangiography will enhance film quality, reducing the incidence of false-negative interpretations. The accuracy of this concept is currently under evaluation in a prospective study at this institution.

MEDICAL DISSOLUTION OF GALLSTONES

DR. SCHOENFIELD: Until recently, surgical operation has been the only definitive treatment for cholelithiasis. Rewbridge[99] in 1937 and Cole and Harridge[100] 20 years later reported the disappearance of gallstone "shadows" by cholangiography in patients treated with mixtures of bile acids. However, only in the past decade, as the understanding of the pathogenesis of cholesterol gallstone formation increased, has a systematic study of medical therapy been undertaken.

Chenodeoxycholic Acid

Danzinger and co-workers[20] showed that chenodeoxycholic acid decreased the cholesterol saturation of bile and dissolved radiolucent gallstones. They administered this bile acid to seven women with asymptomatic radiolucent gallstones visualized by oral cholecystography. In two years, stone size decreased significantly in all patients, with complete dissolution occurring in four. Three subsequent clinical trials[101-103] (two of which were controlled) showed about 60 percent efficacy of chenodeoxycholic acid in dissolving radiolucent gallstones. The rate for spontaneous disappearance of gallstones is less than 1 percent per year; spontaneous disappearance cannot explain the gradual diminution in gallstone size that occurs during therapy with chenodeoxycholic acid. Radiopaque stones have not responded.

The dose of chenodeoxycholic acid in the

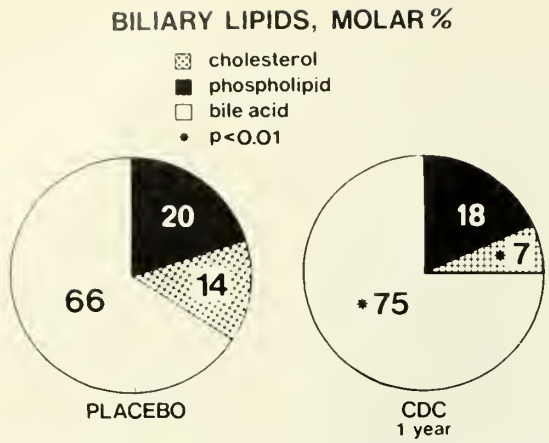

Figure 8.—Composition of biliary lipids in gallstone patients after one year of chenodeoxycholic acid treatment (750 mg per day), expressed as molar percentages of bile acids, phospholipids and cholesterol, totaling 100. In response to therapy, the molar percentage of bile acids increased significantly ($p<0.01$) and the molar percentage of cholesterol decreased significantly ($p<0.01$). (Reprinted with permission from Viewpoints on Digestive Diseases.[101])

therapeutic trials[104] ranged between 750 mg and 4.5 grams daily for 6 to 30 months. The 750 mg dose was as effective as higher doses in decreasing the cholesterol saturation of bile (Figure 8) and causing stone dissolution. Even lower doses of chenodeoxycholic acid (250 to 500 mg) have been found to decrease the saturation of bile, but their ability to dissolve gallstones has not yet been tested.

Within three months after gallstones disappear and treatment is discontinued, bile again becomes saturated with cholesterol. Moreover, recurrence of gallstones has been noted in about 10 percent of patients one year after treatment is discontinued. Accordingly, prophylactic therapy will be necessary at least for some patients after dissolution.

Adverse Reaction

The daily administration of 1 gram or more of chenodeoxycholic acid is often associated with diarrhea. This side effect is the result of the bile acids stimulating the colonic mucosa[105] to secrete water and electrolytes (probably mediated by the cyclic adenosine monophosphate (AMP) system). Lowering the dose to less than 1 gram per day generally obviates this effect.

Thistle and Hoffmann[102] reported that in a third of the patients studied chenodeoxycholic acid was responsible for a twofold transient rise in transaminase, which returned to normal when therapy was continued. Bell and associates[101] observed only minor changes in isocitric dehydrogenase, with no change in transaminase or alkaline phosphatase. Results of liver biopsies of patients receiving chenodeoxycholic acid have shown minor abnormalities in about 20 percent: fatty infiltration in the parenchyma and round cell infiltration in the portal tracts. Coyne and colleagues,[103] however, found this prevalence not significantly different from that reported in untreated patients with gallstones. They concluded that morphologic abnormalities, when found in the livers of patients treated with chenodeoxycholic acid, result from the gallstones rather than from the treatment.

Nevertheless, the effect of chenodeoxycholic acid on the liver in animal studies raises the possibility of hepatotoxicity, which has not been apparent in the limited clinical experience. Webster and co-workers[106] fed chenodeoxycholic acid, 20 mg per kg of body weight, to three rhesus monkeys for four months. The serum transaminase increased in all three and, at autopsy, triaditis was observed in one, with normal hepatic morphology in the other two.

Chenodeoxycholic acid may cause hepatic injury either by a direct action on the liver or indirectly by its bacterial metabolite, lithocholic acid. Coyne and colleagues[103] found in man that the percentage of nonsulfated lithocholic acid in bile increased 360 percent with treatment, whereas Webster and co-workers[106] showed an even greater increase in rhesus monkeys. The effect in humans of chenodeoxycholic acid on the concentrations of sulfated lithocholic acid in the bile and the lithocholic acid in the liver has not been determined. Because sulfation of lithocholic acid has been shown in rats[107] and in humans[108] to enhance its fecal excretion, factors stimulating sulfation may afford protection from increased amounts of lithocholic acid. More investigation is necessary to ascertain how chenodeoxycholic acid administration affects lithocholic acid metabolism and whether this treatment is hepatotoxic in humans.

Although there has been theoretical concern that bile acid therapy might increase the total body pool of cholesterol and thereby increase the risk of atherosclerosis, there has not been an increase in serum lipids in any of the clinical trials. In patients with gallstones, bile acid administration was associated with a decrease in cholesterol pools[109] and with a decrease in the activity of HMG CoA reductase (the rate-limiting enzyme

of hepatic cholesterol synthesis).[30] In addition, two studies reported that bile acid administration was associated with a decrease of serum triglycerides.[110]

Mechanism of Action

In patients with gallstones, chenodeoxycholic acid treatment expands the bile acid pool[20] while decreasing endogenous hepatic bile acid synthesis.[30] Expansion of the bile acid pool results therefore from the exogenous administration of chenodeoxycholic acid. Cholic acid feeding also expands the bile acid pool, but does not cause desaturation of bile or dissolution of gallstones.[102] Chenodeoxycholic acid decreases hepatic cholesterol synthesis[30] and, in contrast to cholic acid, decreases biliary cholesterol secretion.[111] Chenodeoxycholic acid thus exerts its salutory effect on biliary lipids through a dual action of expanding the bile acid pool and decreasing hepatic cholesterol synthesis and secretion (Figure 9).

Gallstone dissolution has required 6 to 30 months of therapy. Desaturation of bile in response to chenodeoxycholic acid occurs rapidly, but the transfer of cholesterol from the stones to the bile is the rate-limiting phenomenon. Slow dissolution or failure occurs particularly with large stones and with those that are radiopaque. Gallstone dissolution is most rapid with pure cholesterol gallstones and is retarded by the presence of compounds that increase the interfacial barrier.

Other Agents

In patients with gallstones, phenobarbital decreases the cholesterol saturation of bile, but less effectively than does chenodeoxycholic acid.[103] Cholesterol crystals disappeared in every case, but no significant decrease in gallstone size was observed. Although the investigators concluded that phenobarbital alone was ineffective in gallstone dissolution, they speculated that this drug might be effective as an adjunct to bile acid therapy or as prophylaxis in patients who are considered to be at high risk. Phenobarbital may exert its salutory effect on biliary lipids by enhancement of hepatic bile acid synthesis and expansion of the bile acid pool.[30,112] In contrast to chenodeoxycholic acid, however, phenobarbital stimulates hepatic cholesterol synthesis;[30] perhaps this explains why this agent is less effective than the bile acid in decreasing biliary cholesterol saturation.

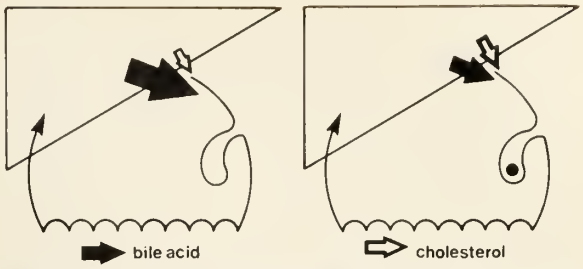

Figure 9.—Diagram of enterohepatic circulation in normal subjects (left) and in patients with gallstones (right). Compared with normal controls, patients with cholesterol gallstones have decreased synthesis and pool size of bile acids, and increased synthesis and secretion of cholesterol. Chenodeoxycholic acid decreases the cholesterol synthesis and secretion, and expands the bile acid pool, rendering bile unsaturated and slowly dissolving gallstones.

Oral administration of lecithin has been proposed as a method to decrease biliary cholesterol saturation. This agent, however, is hydrolyzed in the intestinal tract by pancreatic phospholipase, and only a small amount is reexcreted in the bile. Nevertheless, in one uncontrolled study,[113] oral administration of large doses of lecithin to postcholecystectomy patients with T tubes decreased the cholesterol saturation of bile. Gallstone dissolution, however, has not occurred with lecithin treatment.

Glycerophosphate administration increased biliary phospholipids in rats[114] and decreased biliary cholesterol saturation in nine of ten patients.[115] Further investigation is necessary to determine the safety and efficacy of glycerophosphate treatment for gallstones.

Several therapeutic dietary manipulations have been studied but not yet tested for gallstone dissolution. Bran increases the percentage of chenodeoxycholic acid in the bile and expands the chenodeoxycholic acid pool. A high-fiber diet improves cholesterol solubility in bile. The proportion of unsaturated or saturated fat in the diet, however, did not influence the cholesterol solubilizing capacity of bile.

Future

A simple method for the identification of the prestone state is needed to facilitate population screening. Cholesterol saturation of bile is a prerequisite for gallstone formation, but the ultimate lithogenic phenomena have not been identified. Consequently, a better understanding of the roles of the gallbladder and the enterohepatic circulation in the production of saturated bile and of

cholesterol crystallization and gallstone growth are needed.

Treatment of gallstones with chenodeoxycholic acid has shown the feasibility of medical dissolution, but this therapy is still experimental. Efficacy is virtually certain; safety remains to be shown in a large-scale controlled clinical trial. Investigation will determine whether long-term treatment with this agent is hepatotoxic in humans and whether susceptible patients can be identified prospectively. Also, criteria must be developed to predict individual success or resistance to therapy.

If chenodeoxycholic acid is proved to be effective and safe, appropriate indications for prophylaxis and therapy and the need for treatment after dissolution will have to be determined. Concurrently, other therapeutic or adjuvant agents should be pursued. Finally, a controlled comparison between the results of cholecystectomy and medical dissolution will be required.

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Refer to: Dermatomyositis—Medical Staff Conference, University of California, San Francisco. West J Med 124:316-322, Apr 1976

Dermatomyositis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *One of the most puzzling disorders with which we must occasionally be concerned is that which is categorized uneasily as "polymyositis" or "dermatomyositis." We have such a case for presentation today. The discussion will be by Dr. Lawrence M. Tierney, Jr., Assistant Chief of Medicine at the Fort Miley Veterans Administration Hospital. The case will be presented by Leon Axel.*†

Case Summary

A 59-year-old white man was admitted to the University of California Medical Center for evaluation of dermatomyositis. The patient's illness began three years previously when dysphagia, weakness and generalized edema developed. Results of evaluation by his private physician showed abnormal levels of serum enzymes including elevated lactic dehydrogenase, serum glutamic-oxaloacetic transaminase and creatine phosphokinase. A cine-esophagram showed hypomotility with aspiration. He was referred to the University of California Medical Center for evaluation. His past medical history was remarkable only for coronary artery disease.

On physical examination, the patient appeared chronically ill. An erythematous maculopapular rash over the trunk and upper extremities, periorbital edema and a reddish discoloration of the upper eyelids were noted. There was pitting edema of upper and lower extremities with some tenderness to palpation and pronounced proximal weakness. Laboratory data included hemoglobin of 11 grams per liter, leukocyte count of 11,600 per cu mm with a normal differential, erythrocyte sedimentation rate of 60 mm per hour, creatine phosphokinase of 880 IU per hour, lactic dehydrogenase of 645 IU per liter and aldolase of 22 IU per liter. Alpha fetoglobulin and carcinoembryonic antigen determinations were negative. Findings on muscle biopsy and electromyography were interpreted as consistent with myositis.

Treatment was started with high dose steroids, and there was mild improvement in strength and levels of enzymes and the erythrocyte sedimenta-

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tion rate returned to normal. Persistent dysphagia necessitated tracheostomy and use of a nasogastric feeding tube.

The patient was discharged to a rehabilitation hospital two months after admission. Continuing dysphagia and aspiration led to use of a gastrostomy tube for feeding. There were multiple steroid complications including vertebral compression fractures, cataracts and skin infections. One year ago therapy with methotrexate was started, 20 mg per week given intravenously. Coinciding with tapering of the steroid dosage, there was a gradual, mild increase in the patient's strength. One month before this admission, an erythematous rash developed over the entire body. Administration of methotrexate was discontinued. The patient experienced progressive weakness and was referred back to the University of California Medical Center for reevaluation.

On physical examination, vital signs were found to be normal. A dusky rash over the patient's face and upper trunk was noted. Small bilateral cataracts were seen to be present. Stool specimens were guaiac positive. Periungual telangiectasias and pronounced proximal muscle weakness were found on examination of the extremities; there was weakness of the neck flexors as well. Findings on laboratory studies showed hematocrit reading, leukocyte count and differential to be within normal limits. Erythrocyte sedimentation rate was 6 mm per hour and serum muscle enzyme levels were only slightly elevated. Results on upper gastrointestinal series showed the presence of an active duodenal ulcer. Myopathy consistent with inflammatory or steroid causes was shown on an electromyogram. A skin biopsy of the upper extremities gave findings consistent with dermatomyositis.

Administration of methotrexate was begun without any evidence of hypersensitivity reaction and the patient was discharged on a regimen of steroids and weekly intravenous injections of methotrexate. His condition has been stable since, except for one episode of mild bleeding from the duodenal ulcer.

DR. TIERNEY:* Though the case we have just heard about surely provides a textbook picture of dermatomyositis, this term will be used interchangeably with polymyositis during this talk. Comments about the case will be made where relevant. In reviewing the literature on this subject, one finds a great deal of anecdote and impression with a limited amount of precise information. This is due mainly to a poor understanding of the disorder's causative factors and pathogenesis, and to its relative rarity. Our concept of polymyositis should be subject to continual revision as knowledge of it increases, and artificial classifications should be abandoned readily when no longer useful.

The caveat aside, it can be agreed that polymyositis and dermatomyositis cover a wide spectrum of related disorders, characterized by inflammation and degeneration of varying amounts of skeletal muscle, with a clinical sine qua non of muscle weakness.[1-3] In many patients with polymyositis and dermatomyositis, features of other rheumatic diseases will be noted, but in many others these features will not be present. Additional cases will occur in concert with malignancy, a relationship recently challenged but probably still valid. As suggested, there are various classifications of this disease, the most widespread being Pearson's classification[2] which appears in the *Primer on the Rheumatic Diseases*.[4] This will not be discussed here since it would not add much to our comprehension. If you remember that we are dealing with an inflammatory disease, that there is a loss of strength in all patients with the disease, that there may or may not be a skin rash, that there may be overlap with other related conditions and that there may be associated carcinoma, no further categorization is needed. It may well be that this clinical heterogeneity merely represents host variability to common or similar causative agents. One can imagine that tuberculosis, before its cause was discovered, may have been similarly puzzling to clinicians of old; the same organism may cause a wide range of syndromes, from positive findings on a skin test to miliary disease. This emphasizes how important it is to know the cause of any illness, since without this knowledge there can be no real understanding.

Unlike ankylosing spondylitis, a disease of antiquity observable in mummies, but like rheumatoid arthritis, which has appeared relatively recently in man's evolution, this seems to be a "new" disease in the history of medicine. The first case of polymyositis was recognized by Wagner in 1863, and until about 1950 it was thought that in all cases skin lesions were present (that is, dermatomyositis). We now know that most patients do *not* have skin lesions (a report of 1887

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TABLE 1.—*Percentage of Clinical Signs and Symptoms in 200 Cases of Polymyositis*[1,2,4]

	Percent
Musculoskeletal	
Weakness	
Proximal muscles	
Lower extremities	95
Upper extremities	76
Distal muscles	27
Neck flexors	62
Dysphagia	47
Facial muscles	6
Extraocular muscles	2
Pain or tenderness	48
Arthritic or rheumatic features	24
Skin	
"Typical" dermatomyositis	44
"Atypical" features	20
Raynaud's phenomenon	30

TABLE 2.—*The First Symptom in 100 Cases*[1,2]

	Number
Muscular Weakness	
Legs	44
Arms	8
Dysphagia	2
Skin rash	24
Joint or muscular pains	15
Constitutional	7

making this point was disregarded). The disorder was first referred to a pseudotrichinosis, which it most resembles phenotypically though not clinically. The advent of muscle biopsy has helped separate this entity from other myopathies, especially the dystrophies, although for accurate results impeccable technique and careful handling of the specimen are necessary. The first allusion to a kinship with malignancy was noted in 1916.

While epidemiologic studies[5] have shown no susceptible group geographically, they have at least shown that there are two peaks in age of incidence—one in early childhood, the second in the fourth and fifth decades. Five new cases per million population occur yearly, a rate similar to that of polycythemia vera. There is no familial pattern or associated histocompatability antigen. In both incidence peaks there is a 2:1 female predominance, in both pure and overlap cases. The picture can vary from the explosive onset of profound weakness, heliotrope rash, and systemic complaints on the one hand, for example, to the gradual development of slight pelvic girdle weakness over several years on the other. Table 1 shows the range of signs and symptoms gleaned collectively from several series.

First let us consider the strictly muscular syndromes. It would appear that a good rule of thumb is "no weakness, no diagnosis." In most cases, onset of weakness is subacute and symmetrical, the proximal muscles of the lower extremities usually causing early complaints such as difficulty in climbing stairs or boarding a bus. Upper extremity problems may be noted, for instance, when a patient attempts to comb the hair. The frequency of affliction of neck flexors is important to remember in the physical examination.

Weakness of the facial and extraocular groups is very unusual, and therefore so is diplopia. Dysphagia, however, via dysfunction of the striated pharyngeal musculature is not, as we have heard. Dysphagia and resultant aspiration tend to be prominent in more acutely developing cases, and are more often linked with poor prognosis. Fortunately, respiratory paralysis is hardly ever encountered except in the most aggressive forms of the disease. The presence of pain and tenderness is not essential for diagnosis. Atrophy and contractures are likely to occur, largely when treatment has been delayed or is ineffective.

Some precipitating factors apparently exist. Older papers comment on the role of the menopause, but this is doubtless an artifact given the peak age incidence and sex predilection for women. Infections, trauma and systemic stress are said to bring it on, but this is in no way distinctive for polymyositis. We have now discussed the *range* of muscle symptomatology, but the *first* symptom is likewise of note (Table 2). This is of a muscular nature in 69 percent of patients, but dermatologic in 24 percent. The remaining 7 percent often provide diagnostic dilemmas; I have personally seen polymyositis manifest as a fever of unknown origin (FUO), and Barwick and Walton[1] have documented similar atypical presentations.

Raynaud's phenomenon occurs in 30 percent of cases in some point in the course. Careful analysis of this symptom in polymyositis discloses that it correlates best with the presence of an overlap syndrome, in the main when elements of scleroderma are encountered as well as those of myositis. The same is true of arthritis, that is, it is unusual in pure polymyositis or dermatomyositis, but fairly frequent when hints of another rheumatic condition are detectable. Concerning overlap, criteria should be considered individually for the diagnosis of each condition when more than one is suspected.[6] Confounding the issue is the

lack of universally accepted criteria for this type for polymyositis—such as already exist, for example, in the disorders of rheumatoid arthritis and lupus erythematosus.

The typical rash of dermatomyositis is seen in 40 percent of cases. It is a dusky eruption in the malar and periorbital distribution; in the latter area it is referred to as the heliotrope. This may extend onto the upper thorax in a V-shaped pattern. Noteworthy when present are hyperemic patches which may be slightly raised and scaly and found on the elbows, knuckles and malleoli. These are called Gottron's papules. The rash can be precipitated or exacerbated by exposure to sun. As has been pointed out, such a rash is the initial manifestation of dermatomyositis in most patients. In rare cases, this dermatologic feature alone may be present for several years without the evolution of muscle weakness.

Less specific than these findings are the subcuticular telangiectasias which are visible grossly on occasion, but which are more striking when viewed through a drop of oil with an ophthalmoscope at +20 to +40 diopters. Similar abnormalities of the capillary loops occur in rheumatoid arthritis, systemic lupus erythematosus and progressive systemic sclerosis, and it is said that astute diagnosticians can even distinguish among these diseases by certain subtle differences at capillarioscopy. The cuticle of the nail, whether or not there are telangiectasias, may be reddened, roughened, irregular and hyperkeratotic, even in the absence of overzealous manicuring. These nail changes are instructive to look for, and are clearly useful to clinicians.[7,8]

In summary, (1) the weakness is proximal, usually starting in the legs; (2) the rash when present is very distinctive; (3) there is dysphagia in the more severe cases; (4) Raynaud's phenomenon and arthritis are more likely to occur when aspects of other rheumatic diseases are concomitantly present.

What then of inflammatory myopathy associated with a malignancy? It is taught in the textbooks that when dermatomyositis is found in a male over the age of 40, there is a 50 percent likelihood of an associated tumor being present. The basis for this deduction comes from a few small studies done in about 1940 in which the diagnosis of polymyositis was only speculative, there being no biopsy technique or enzyme studies available. Any one of a number of neuromuscular complications of carcinoma or other conditions have been present in these selected series. Well-documented instances of polymyositis associated with a tumor are infrequent in the literature. Nonetheless, most authorities do agree that the instances of such association are more numerous than would be accounted for by chance alone.[9]

Where well studied, the myositis has tended to precede the tumor, often by years, and a rash (that is, dermatomyositis) was found more often than in spontaneous cases. The opinion still exists that tumor-associated myositis pursues a more virulent course than polymyositis and is steroid-resistant, though ample proof of these observations is wanting. Cure of cancer has resulted in remission of the associated dermatomyositis. In cases of dermatomyositis an extensive search for hidden malignancy is unwarranted and likely to be unrevealing unless there are findings on clinical examination that point to a specific organ system. In patients with dermatomyositis and cancer who die, death results from the muscle disease in about half the cases and is the direct effect of the tumor in the remainder. Despite the putative autoimmune basis of all of the rheumatic diseases, it is only polymyositis that has been linked with a higher incidence of many different types of tumors. As to other organs, interstitial pneumonitis and cardiac muscle infiltration are observed in a small percent of nonoverlap polymyositis.[10,11]

What other diseases can produce proximal weakness with suggestive findings on laboratory tests? Muscular dystrophies, when confined to the girdle muscles, may appear in adults like polymyositis, but the family history is positive and findings on muscle biopsy do not show inflammation to be present. Myasthenia gravis, potentially proximal, affects muscles used the most (like the external ocular muscles), responds to edrophonium, has normal serum enzymes and shows electromyogram (EMG) fatiguing. Almost any endocrine disorder (too much or too little hormone) can cause this pattern of weakness. The major entity meriting serious consideration is thyrotoxic myopathy. This may be exceedingly cryptic and indistinguishable from polymyositis, especially in older patients where no other findings of thyrotoxicosis may be found. You need only to think of it for diagnosis.

Steroid myopathy is easy to dismiss when it is primary, but not when a patient is being treated with these agents exogenously for a disease which itself can cause weakness. This thorny problem

was encountered in today's patient. The electromyography tracing is not altered in steroid myopathy in contrast to other myopathies, but this may already be abnormal from the disease under treatment. One may be forced to decrease dosage temporarily and observe for response. Fluorinated compounds like triamcinolone are perhaps more culpable. No precise correlation between duration and dose of steroids and occurrence of myopathy is observed. As another cause of proximal muscle weakness, rhabdomyolysis can be seen as an acute event secondary to binge drinking or to muscle compression of any cause, but here weakness is less prominent than are the very high levels of muscle enzymes in the serum.

The polymyopathy of hypokalemic periodic paralysis is most striking in adolescence, but may reappear in middle age as indolent weakness. Findings on biopsy are distinctive, showing vacuolization and hydrops of the myocytes. The absence of visible fasciculations excludes lower motor neuron disease, itself typified by distal loss of strength rather than proximal. Long tract signs can be in evidence. In any patient with weakness of all four extremities, no matter how obvious the cause may seem, cervical spine films should be made in the first evaluation to exclude remediable lesions such as osteoarthritic spur. As for infectious (or pseudoinfectious) causes, sarcoidosis is the only process which gives a true proximal *weakness,* and granulomata are found on biopsy studies. These are a few important differential considerations, and many others may be found in the literature.[12]

Given clinical features that suggest polymyositis, what is the best way to use laboratory tests in confirming this suspicion? A systematic approach to this problem was presented in a paper by Vignos and Goldwyn,[13] who looked at the utility of tests commonly used in diagnosis and management of fairly well-documented cases. The four most valuable are determination of serum levels of muscle enzymes, urinary creatine measurement, muscle biopsy and electromyography (the first two being most useful in following therapy). Antinuclear antibodies are consistently negative despite superficial resemblance of the heliotrope to lupus erythematosus (LE).

Creatine, the anhydride of which is creatinine, is synthesized in the liver, is stored in muscle and is normally present in small amounts in the urine. In any organic disease of muscle, urinary excretion of creatine rises and in this series all patients had greater than a "6 percent creatinuria" expressed as the concentration of urinary creatine over the sum of concentration of urinary creatine plus creatinine. Besides use in initial diagnosis, this was the first aberration to appear during relapse under therapy, occurring before the rise in serum enzymes.

Of the serum enzymes, creatine phosphokinase (CPK) is the most sensitive, elevated in more than 80 percent of cases. Levels of CPK may be normal now and then in biopsy-proven cases, especially early in untreated patients and late in the course of the disease when widespread fibrosis and atrophy have supervened. The measurement of transaminase and aldolase is popular in some hospitals, but these enzymes have the disadvantage of being found in other tissues. Naturally, studies of muscle enzymes are convenient to obtain too, and findings can be used in assessing therapeutic endeavors. Just as the creatine levels in urine rise during exacerbations, these serum enzyme levels rise before weakness occurs and fall before strength returns in responsive cases. Bear in mind that these changes in enzyme levels occur later than urinary creatine change.

For biopsy, pick a muscle that is weak, and one in which an electromyography needle has not been used because it is important to know that inflammation is not iatrogenic. There are two types of skeletal muscle fibers which are hard to tell apart by light microscopy but are different physiologically. The first type, which mediates most routine muscle contractions, operates aerobically and at slow speeds, generates little force, but is indefatigable. The second type of fiber produces greater force, but for short periods and often anaerobically. The typical biopsy findings show fiber degeneration and attempts at regeneration indicated by basophilia and varying fiber size and round cell infiltrates. Nuclei are large and central. Cell infiltration is said to be less prominent if there is an associated malignancy.

For me an electromyogram is exceeded in complexity only by an electroencephalogram (EEG)—in patterns, terminology and interpretation. It promises to remain safely within the diagnostic domain of the neurologists. You will read of the myopathic triad of fibrillatory potentials, polyphasic bursts on voluntary contraction and pseudomyotonia. A few words of explanation might help. In muscle disease the electrical pattern is an active one since many units are required to do the same amount of work that nor-

mally would be done by a few. The contraction of abnormal fibers gives electromyographic deflections which are smaller and shorter, somewhat "moth-eaten" in appearance. The normal fiber potential on voluntary contraction is bigger and shorter, and has less than four phases. Diseased potentials typically have more than four and thus are polyphasic, in addition to being more numerous. Fibrillation, however, and pseudomyotonia are types of involuntary activity that can be noted with nonspecific nerve or muscle injury. Normal muscle records no activity during resting. Since dermatomyositis is a patchy disease, both biopsy and electromyography are subject to sampling error and on occasion give normal finding. In difficult cases the paraspinous muscle group of the back may be the only area abnormal electromyographically.[3]

In summary, a reasonable approach to the investigation of a patient with muscle weakness might be (1) measure urinary creatine and the serum level of muscle enzymes because an abnormality will indicate myopathy, albeit nonspecifically; (2) then proceed to biopsy and electromyography, picking an abnormal site based upon areas of weakness; (3) should findings on the latter two studies be normal or nondiagnostic, then the appropriate search for other causes of myopathy can be carried out. When all else fails, observation and repeat testing should give the right answer.

Now I would like to turn to a speculation or two upon the causative factors and pathogenesis of the perplexing disorder. The association with malignancy adds further interest. Does the tumor make a substance that is toxic to muscle? Does the immune mechanism attempting to eradicate the neoplasm cross-react with muscle? Does the same agent (a hidden virus?) cause both or either independently? It remains uncertain. Virus-like particles of various structural types have been detected in the myocytes of patients with polymyositis by electron microscopy. Circulating antibodies to muscle may be found after any muscle injury, but a recent report describes immunoglobulin and complement deposits in vessel walls of patients with polymyositis.[14] Such deposits are observed mainly in children in whom this disorder behaves like a vasculitis, a feature more compatible with circulating immune complexes. Two patients with agammaglobulinemia have been described as having polymyositis suggesting that gamma globulin is not required in all cases. Typical dermatomyositis has occurred in a patient with C2 deficiency,[15] indicating that the classic pathway of complement activation is not always required either. Such immune deficiencies might render the patient more susceptible to other immunological injury, for various rheumatic diseases have occurred among persons with various deficiencies of the complement system.

Cell mediated immunity may have a role in polymyositis in adults. Lymphocytes from patients with active myositis cause cytotoxic changes when layered upon autologous or chick muscle cells in culture.[16] These cytotoxic changes were interpreted as secondary to T-cell production of lymphotoxin, a lymphokine recognized as a participant in delayed hypersensitivity. Such damage at the membrane or subcellular level might account for diffuse clinical weakness when only patchy changes are seen on pathological specimens. The soluble mediator of injury (lymphotoxin) was postulated to diffuse through the tissues and to injure sarcolemma of remote fibers, without a cellular response that would need only to be present at the site of the instigating antigen. The antigen could be part of the muscle but need not be, as it as easily might be a fellow traveler located in that tissue. All this remains speculative. In short, there are many tantalizing suggestions as to the immunological or viral (or both) causative factors in this disease.[17-19] Some proven viral diseases, such as influenza B, may cause muscle pain and swelling with notably elevated levels of serum enzymes, but without weakness. Other myolytic states may show very high levels of enzymes with preservations of strength. These observations lend further credence to the notion that weakness in polymyositis is due less to the actual amount of necrosis than it is to some physiologic derangement.

How should polymyositis be treated? Winkelmann reviewed statistics from the presteroid era from the Mayo Clinic experience,[20] and contrasted them with those from patients given corticoids. Polymyositis undergoes spontaneous remission in many patients and there exists no proof that steroid therapy increases this rate of remission. This author did conclude that steroids hasten remission, and therefore avert contractions and atrophy, surely a benefit. It is not clear that the groups are well defined in this retrospective study, but the conclusions have not been refuted.

Death from polymyositis occurs most frequently in the first two years. The outlook is

worse when aspiration occurs,[21] and this observation is applicable to today's patient. Empirically, therapy with steroids is begun at about 60 mg of prednisone per day, without reduction in dosage until levels of serum enzymes are normal and urinary creatine reduced by half. One also follows muscle strength. Therapy should not be thought a failure until a four month trial has been administered. In the face of a poor response, or development of intolerable complications of corticoids, immunosuppressive agents have been used. Methotrexate has been most widely used,[22] but a variety of other agents have been tried. As in today's patient, methotrexate is given in relatively small doses by vein. In this way the drug bypasses the portal circulation, perhaps reducing hepatotoxicity. You cannot help but be concerned about giving immunosuppressive drugs of this type for a condition that is usually benign. My own experience in the immunosuppressive treatment of polymyositis has been quite favorable in the short-term. The long-term effects are still uncertain. I cannot disagree with the use of such therapy for the patient being discussed today because of the severity of the illness.

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Important Advances in Clinical Medicine

Epitomes of Progress—Ophthalmology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Ophthalmology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Ophthalmology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Ophthalmology of the California Medical Association and the summaries were prepared under its direction.

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Senile Macular Degeneration

SENILE MACULAR DEGENERATION (SMD) is the leading cause of reduced visual acuity, and occurs particularly in older persons. In the Model Reporting Area (MRA) of the United States, SMD accounted for 19 percent of all newly reported cases of blindness. In Great Britain, SMD is the cause of 25 percent of all newly reported cases of blindness, and its prevalence with age is most impressive in that SMD accounts for only 1 percent of the causes of blindness in people less than 60 years of age, but 36 percent of those over 70 years of age.

The macula is the very specialized portion of the central retina. It is responsible for fine discriminating visual acuity. In fact, acuity better than 20/200 is achieved only by the macula. "Form vision" is obtained from the peripheral retina. The most frequently observed clinical finding in an eye with SMD is hypopigmentation of varying appearance in the macula. These pigmentary alterations can be so subtle as to be at the limit of resolution even with the magnification provided by the slit lamp biomicroscope and fluorescein angiography. If progression is characterized by hypopigmentation only, then the resulting appearance may be similar to geographic atrophy. Fluorescein angiography has been particularly helpful in distinguishing such atrophic types from a more exudative type characterized by hemorrhage, serous exudation and cicatrization. Serous detachments of the retinal pigment epithelium (RPE) may change within hours, but it is more common for those lesions to gradually evolve over several months. The appearance of a grey-green mound in the previously hypopigmented area is a poor prognostic sign since this is related to subretinal neovascularization and hemorrhage. This neovascular tissue is the source of abnormal leakage, which can lead to serous detachment of the sensory retina or RPE, or both. In addition, hemorrhage and subretinal lipid may be the early manifestations of such subretinal neovascularization. The macular lesion may take a rounded or so called "disciform" shape with the development of cicatrization. Since SMD may masquerade as an intraocular tumor, some eyes have been obtained for histopathologic correlation. The histopathology is correlated with fluorescein angiographic findings to provide the basis

for the hypothesis of Gass and others regarding the pathogenesis of SMD.

The role of therapy, particularly photocoagulation, whether xenon-arc or argon laser, has been the subject of much interest and controversy. Photocoagulation therapy is directed toward elimination of serous detachments or the eradication of the abnormal subretinal neovascular network. This therapy must be applied before involvement of the vascular free zone (the center of the macula), or else the scar from therapy will be as detrimental to the patient as that from the disease. In general, the results of such therapy have not been encouraging, since in many cases the disease process is already too far advanced at the time of therapy. In reported series, the various forms of therapy have been said to yield success rates varying from 18 to 43 percent. These series are greatly biased by the criteria for therapy of the different investigators. All authors agree that no statistically significant conclusions can be drawn since no double-blind study has been done. A study currently in progress suggests that this therapy is of value in holding the patient's vision at the same level as at the time of photocoagulation, whereas the untreated controls undergo subsequent deterioration of vision.

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Visual Field Testing

THE MOST IMPORTANT ADVANCES in visual field testing that have occurred within the lifetimes of today's practicing physicians can be attributed to the efforts of Goldmann, Harms and Aulhorn. Recognizing certain inherent limitations in quantifying the variables of tangent screen perimetry, Goldmann sought to improve upon that technique by building a hemispheric dome-shaped perimeter according to precise specifications. With this device, accurate patient fixation is fully monitored through a telescopic viewing device which the perimetrist uses throughout the testing procedure. In addition, the illumination is accurately determined by frequent calibration of the single bulb which, by means of filters, is projected for dual use as the target as well as the background light source. Additional neutral density filters are also used to vary the target luminance so that the intensities of different presenting targets have a constant relationship to each other that may be as small as 0.1 log unit difference. This perimeter also has the advantage of employing variable target sizes which intermix with the luminance levels to provide even more combinations of stimuli than can be achieved by intensity variation alone yet they maintain a precise mathematical separation between each setting. Another convenience of this machine is the pantographic arm which moves the target location throughout the dome and allows exact point-for-point notation on the visual field paper being marked by the perimetrist. A number of copies of this instrument made by different manufacturers are now available but none surpass the original concept.

Although this perimeter greatly improved the reliability of kinetic perimetry, complete static perimetry (an even more sensitive measure of the visual island) remained too cumbersome to carry out, even with Goldmann's device. The reason for this difficulty is the need to present many levels of target illumination at a large number of testing points during the examination. The rapid manipulation of at least three filter levers, which is necessary to achieve the proper combinations, is just too complicated when done manually. Harms and Aulhorn recognized this problem and produced an instrument with automated filters which are moved by a hand-held control box. The successful introduction of this improvement over Goldmann's original design has permitted ultimate precision in visual field testing and has already increased the depth of existing knowledge on the subject of visual field abnormalities. Because of these perimeters, the ability of the physician to separate the stage of ocular hypertension without scotomata from the onset of glaucomatous field damage has finally achieved a level of accuracy in which he can be fully confident.

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Absorptive Lenses

It has been estimated that 200 million Americans use sunglasses either for cosmetic appearance or in an attempt to increase their vision. Certainly, people who have had surgical operation for cataracts and therefore no longer have the natural barrier to radiation, particularly to ultraviolet, can greatly benefit from absorptive lenses. But does an average person really see better with sunglasses? This is a complicated question and depends on many factors, the most important of which is the general level of illumination. In dim light, such as evening or indoors, visual acuity improves with increasing illumination. Sunglasses, by reducing general illumination, also reduce visual acuity. The argument that they reduce glare of headlights when driving has been disproven by studies showing that the decreased vision predominates over the glare reduction.

In moderate illumination, sunglasses generally neither increase nor decrease vision. When illumination is high, however, results of studies are not clear-cut, but generally suggest that sunglasses improve performance of some visual tasks. One definite beneficial effect of absorptive lenses is on dark adaptation. This process is dependent on the intensity and duration of the preadaptation stimulus; thus sunglasses worn at the beach during the sunny day will allow better visual sensitivity when driving home (without wearing them) in the evening.

Sunglasses also influence color vision; this is a negligible factor with neutral gray lenses and increases with other colored lenses, particularly yellow. The effect is most pronounced for patients who are already color defective in whom it can severely impair their already compromised hue discrimination. This may present a danger to color-deficient persons because of poor recognition of traffic signals. Another potential hazard of sunglasses is in the use of polarizing lenses. The plastic sheet polarizers intended for polarizing visible light are inefficient in the near infrared spectrum and it has been observed that, although glare will be removed from reflected images of the sun by such polarizers, infrared rays will not be absorbed and therefore could be hazardous.

Finally, a new type of phototropic glass has recently attracted considerable attention. This contains silver compounds which darken upon exposure to ultraviolet light and lighten when this radiation decreases. The glass transmits ultraviolet light during the darkening phase and does not filter out the infrared spectrum at any time. The total darkening is generally insufficient for bright lights, so that an additional absorption coating must be added to the back surface of the lens to increase its overall darkening effect. These lenses tend to be expensive and react slowly, especially while lightening after the ultraviolet stimulus is removed.

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Technetium-99 Lacrimal Microscintigraphy

—A New Technique to Evaluate the Lacrimal Drainage System

In 1972 Rossomondo and co-workers described a new method of evaluating *in vivo* the lacrimal drainage system utilizing a minute quantity of technetium-99 radioactive tracer delivered as an eye drop. The progression of the radioactive tear is followed through the drainage system using a gamma camera with a micropinhole collimator. The procedure takes between 15 and 25 minutes (Figure 1). Throughout the procedure the patient

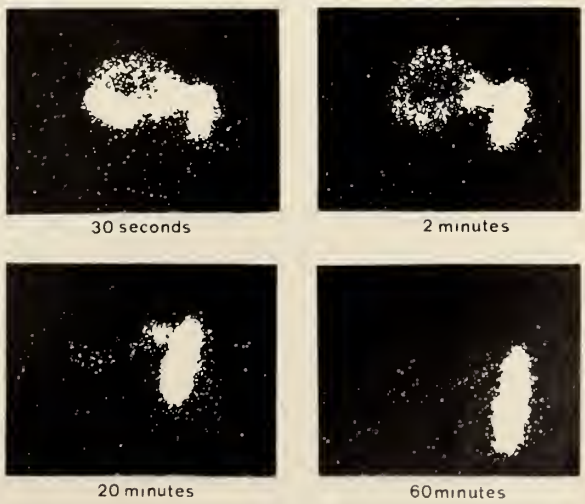

Figure 1.—Technetium-99 microscintigraphy in a normal subject. (Compliments of Dr. D. M. Maurice)

is permitted to blink freely and naturally. The method involves no catheterization and no discomfort to the patient. There is no sampling from the cul-de-sac and no cotton swabs up the nose. Since the canaliculi are not instrumented and the radioactive material is suspended in a sterile buffer normal saline solution, the natural physiologic dynamics of the drainage system are maintained. The radiation dose to the lens is approximately 4 to 6 millirads. This dose is about 2 percent of that received in a single typical anterior posterior skull roentgenogram. The test can be used to study not only pathological alterations in the tear drainage mechanism but also to study the normal physiology of tear drainage. Since the gamma camera is a widely used diagnostic tool found in more than 1,000 hospitals throughout the United States, lacrimal microscintigraphy can be available to ophthalmologists in many nuclear medicine departments.

In a recent study by Chaudhuri and associates, a comparison was made between conventional radiographic contrast dacryocystogram and the radioisotope scan of the lacrimal drainage apparatus (technetium-99 lacrimal microscintigraphy). The investigators concluded that lacrimal microscintigraphy was superior to the routine contrast dacryocystogram. They found it to be particularly useful in analysis of functional blockage; for example, in situations where the "lacrimal pump" is abnormal or in partial stenosis of the nasolacrimal duct. In both conditions the drainage system irrigates freely but does not permit the free passage of tears under normal physiological circumstances. In addition, in functional and in some anatomical blocks, the contrast dacryocystogram which employs direct catheterization of the canaliculi and injection under pressure can create a false passage or open up physiologic or anatomic blocks thus erroneously implying patency. Consequently, the lacrimal microscintigraphy technique is felt to be superior since it is done without catheterization of the canaliculi and therefore permits study of pathological obstruction under physiologic conditions.

In summary, lacrimal microscintigraphy appears to be an excellent method of studying the normal physiological tear drainage as well as tear drainage in various pathological conditions. The procedure is atraumatic and requires no catheterization of the canaliculi or the duct while delivering a small radiation dose to the lens and anterior chamber. Accurate diagnoses of both functional and anatomical blocks can be made. The normal physiology of tear drainage may be studied with the technique. Lacrimal microscintigraphy should allow accurate differentiation between hypersecretion, anatomical block and functional block in patients who complain of epiphora.

A. Ralph Rosenthal, MD

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Computer Assisted Tomography

Computer assisted tomography (CAT), a fundamentally new technique in x-ray diagnosis, has excited widespread interest and enthusiasm since its introduction in 1973. The CAT scan depicts variations in tissue density to a degree that cannot be achieved by conventional radiography. A sodium iodide crystal rather than photographic film serves as the x-ray detector.

The technique is noninvasive and is free of discomfort and risk. The x-ray dose is less than that employed for a regular skull series. Admission to hospital is not required. During a single scanning procedure, a total of 28,800 measurements are taken. A small computer calculates the absorption values of the tissue section being scanned. Values are calculated for tissue blocks measuring 3 by 3 by 13 mm. Even higher resolution systems are now becoming available. The results are displayed on both a computer printout and on a cathode ray tube; the brightness of each block is proportional to its absorption value. The cathode tube display is photographed with a Polaroid® camera and is part of the report sent to the referring physician.

The CAT scan has proved invaluable in the diagnosis of intracranial disease. It has become a major tool for neuro-ophthalmologists investigating such problems as suspected compressive lesions causing visual loss. Not only can intracranial mass lesions be identified but also their probable nature may be determined as well by virtue of their relative density. A distorted ventricular system may provide still another clue to the presence and site of an intracranial lesion.

Ophthalmologists have been increasingly impressed with the help CAT has afforded in the diagnosis of orbital disease. An orbital CAT scan takes 10 to 20 minutes to carry out and the result is available 10 minutes later. The information gained often cannot be obtained by conventional radiological methods, including orbital venography. Meningiomas, optic nerve gliomas and orbital metastases are identified readily. Extensions of orbital tumors into the cranial cavity or extensions of sinus tumors into the orbit may be clearly seen.

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EDITORIALS

Library Resources and Continuing Medical Education

TWO ARTICLES in this issue serve to call attention to the importance and use of library resources in medicine and particularly in the continuing education of practicing physicians. In these days of emphasis on patient care audits and practice audits, and on hours of attendance at formally accredited courses or programs in continuing medical education, it is reassuring to know that recourse to the medical literature is not only readily available, but actually thrives. Physicians, and anyone else for that matter, learn best when they feel a need or are motivated (to use the current jargon) to find out more about a particular subject. This is what occurs when physicians seek out and use library resources. Also, it is likely to be a far more efficient and effective means of getting the information that a physician needs to him when and where he needs it, than is any medical audit or any carefully structured and officially approved course in continuing medical education.

No good way has yet been found to give this sort of continuing medical education the credit it deserves in terms of public accountability for the quality of patient care. But it should be encouraged, and where possible rewarded, and both the National Library of Medicine and the Washington State Medical Association are to be commended for their accomplishments in making it both possible and actually easy for practicing physicians to make greater use of library resources.

—MSMW

The Status of *In Vitro* Preimplantation Embryogenesis

WITH THE CURRENT ATMOSPHERE of growing concern about informed consent, human experimentation and Department of Health, Education, and Welfare regulations of fetal research, the review by Karp and Donahue of the status of *in vitro* preimplantation development, which appears in this issue of the JOURNAL, is timely. The state of the art is presented clearly. For a number of mammalian species *in vitro* oocyte maturation is possible in either serum supplemented or defined media. Human ova likewise have been matured *in vitro,* although they appear to be more fastidious in their culture requirements, and success rates have been notably lower. Fertilization *in vitro* has been accomplished for many lower mammals but has not been verified for human material. There is no case in which a Y chromosome has been shown in an early cleaving human zygote, and the criteria for claiming fertilization have been principally morphologic. Transfer of these presumptive human zygotes to a recipient uterus has never resulted in a successful implantation. Postfertilization *in vitro* culture of subhuman mammalian embryos is rather easily accomplished, but the only work in human embryo culture has been in conjunction with the above-mentioned fertilization attempts. In summary, *in vitro* oocyte maturation, fertilization, embryo culture and even transfer to a pseudopregnant uterus with subsequent birth of normal offspring has been accomplished for subhuman mammals such as mice. However, in humans only the first step of ova maturation *in vitro* has been unquestionably accomplished.

Why continue work along these lines? The clinical goal has been the circumvention of blocked fallopian tubes causing infertility. There are 2½ million childless couples in the United States who might be aided by such techniques. However, I believe that we should heed the suggestion of Marc Lappé, quoted by Karp and Donahue, that more animal experimentation including experience with primates is necessary be-

fore attempting such experiments in humans. It must be shown, at least, that the risk of a birth defect in offspring conceived *in vitro* is not significantly different than for offspring conceived *in vivo*. The use of *in vitro* techniques for sex selection, as suggested by Karp and Donahue, is unlikely. Separation of the X-bearing and Y-bearing sperm with subsequent artificial insemination will be simpler and considerably less risky, less tedious and less expensive. The methodology cited by the authors to achieve prenatal diagnosis of genetic defects is already in use and does not require an *in vitro* mode of reproduction.

From a less clinical view, research on the preimplantation stages of embryogenesis still has significant merit. There is good evidence that 10 percent of human conceptions are chromosomally abnormal. In spite of the fact that this is a significant cause of spontaneous abortion, with 35 to 50 percent of such abortuses being aneuploid, 15,000 chromosomally abnormal children are born each year in the United States. Studies of chromosomal behavior during the peri-fertilization period could provide important insights into the causes of this high rate of aneuploidy. Better understanding of this period of development could provide new avenues for the evolution of contraceptive research, and investigation of the biochemistry of early differentiation and de-differentiation could reap rewards in the understanding of another type of "new growth," cancer.

Much of the discussion of *in vitro* preimplantation development has been motivated by fear—fear of the power that comes with control, fear of science and fear of change. Out of this fear have come arguments that research in *in vitro* embryogenesis will cause us to lose our humanness. I would argue that the willingness to risk the dangers inherent in a changing and improving society is basic to our humanness. The arguments that control is not natural have even less merit. The goal of medicine has been to minimize human suffering by deliberate control. Diabetes is natural, insulin is an instrument of control. In reproductive medicine an early attempt at control was by selective mating. Today we practice positive direct eugenic control with the use of therapeutic abortions, prenatal diagnosis of genetic defects and fetal therapy (intrauterine transfusions). Joseph Fletcher has carried this argument to the extreme of stating that *in vitro* reproduction is more willed, chosen, deliberate and controlled than coital reproduction. Since these traits are essential to humanness he concludes that coital reproduction is less human than *in vitro* reproduction.

The National Committee on Protection of Human Subjects proposed, and the Secretary of Health, Education, and Welfare agreed that regulations regarding *in vitro* fertilization and preimplantation development not be stipulated but to leave these issues to a newly constituted National Ethical Advisory Board. An invitation was proffered for comments on appropriate future regulations. This is the appropriate time to start our ethical inquiries. As our society appears to be expanding from a sanctity of life morality to include a quality of life morality, and as we become a biologically aware society it will be necessary to reconsider many basic ethical issues related to our humanness.

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A BICENTENNIAL EDITORIAL

America in Process of Change

THERE IS GOOD REASON to believe that America is in a process of fundamental change. It is interesting to note that this is occurring without any identifiable leadership or even much discussion. Rather our leaders are looking to the led for some indication or clue as to where the nation may be headed. And such discussion as there is often seems to be somewhat beside the point against the backdrop of the poorly understood forces that appear to be at work.

The evidence that something fundamental is happening is clear enough. It is to be seen in changing attitudes toward virtually all the social institutions that have always formed the fabric of any society or of any nation. The churches, our educational institutions, our legal system, our economic system and even our government are all under attack and all seem unable to deal with the complexities of life in present-day America either effectively or to the satisfaction of the people. Even the institution of the family, which is considered so essential to normal development, maturation, a full and satisfying life and even graceful senescence, seems to be losing much of

its integrity and strength. Public confidence in, and respect for, each of these important social institutions has fallen off sharply according to almost every indicator. Certainly this must be evidence of fundamental change. And to accompany this there has been a growing rejection of some of the assumptions and beliefs that have served us well until quite recently. For example, the idea of limitless growth, unbridled competition, survival of the fittest (with charity for those who could not or did not make it), and even the good old Puritan work ethic itself—all of which served well to help achieve the present standard of living in America—now seem to be losing in the public esteem. There can be no doubt that change is occurring.

But the process of change in America is by no means completed. It seems more likely that it is only just beginning. To be sure the dismantling of much of the social and economic paraphernalia that got us to where we are seems well underway. The manifestation of this can readily be seen in the anti-intellectualism, antiprofessionalism and anti-institutionalism that are so evident everywhere. And the mood is even antibiological when it insists upon the absolute equality of persons when biologically no two persons are ever created exactly the same or equal and when each person has a unique experience with the environment which makes him uniquely different from every other person.

To many all of this may seem retrogressive and even dangerous. But it need not be. One can think of it more as though we have put our ship of state in temporary dry dock and are in the process of stripping it down before remodeling it to sail the as yet uncharted seas of change and progress for another two hundred years or so.

But where might we as a nation be headed? It may be possible to begin to glimpse some of what seems to be emerging for the future. For instance, there is evidence of a growing acceptance of the idea that each person is entitled to certain basics such as housing, income, education and health; to a certain freedom from personal risk (or to compensation for any injury or misfortune that may occur); to a degree of personal fulfillment, and even to share in that something that is beginning to be called quality of life. Most of these entitlements are beginning to be considered rights. Put simply, all of this places the individual person at the center of the stage as the subject of greatest national concern. It patently rejects the material economic ethic of unrestricted free enterprise, unbridled competition and survival of the fittest. It replaces all this with a new societal ethic which is more social than economic in orientation and which must somehow be made to work in an increasingly complex and interdependent technologic, social, economic, political and, yes, biological world.

There is much to suggest that a concept such as this is gaining ground and even that it is already profoundly changing many of the social institutions of this nation. It is conceivable that it could become a new national purpose, one that could keep us as a nation well occupied for the next hundred or two hundred years. Were this to occur it could become the positive force to end the negativism so evident everywhere today. It could become the force needed to restructure and strengthen our social institutions and our social fabric to meet a challenging future.

While the future may or may not develop in the framework suggested above, there can be no doubt that America is in process of change, and there can be no doubt that medicine and health care are to be part of the change. If indeed society is to become more person oriented, and if indeed health, well-being, personal fulfillment and quality of life are among the goals, then medicine has much in the way of knowledge, expertise and experience to contribute. It is not too early for our profession to attend to this—it could be the wave of the future.

—MSMW

Causes and Management of Gallstones

THE "SPECIALTY CONFERENCE" this month is from the University of California, Los Angeles, School of Medicine. It presents a comprehensive look at the pathogenesis, diagnosis and management of gallstones.

Pathogenesis of Gallstones

During the past ten years, there has been an exponential growth in understanding of the pathogenesis of cholesterol cholelithiasis. Although the cause of cholesterol gallstones has not been defined completely, the physicochemical prerequisite for gallstone formation appears to be precipitation of insoluble cholesterol crystals from bile. Cholesterol is solubilized in bile by being carried in mixed micelles of bile salt and lecithin. Thus,

precipitation of cholesterol might result from increased biliary excretion of cholesterol, decreased excretion of lecithin, decreased excretion of bile salts or some combination of these processes.

Biliary cholesterol secretion has been studied in a small number of normal subjects and in a few patients with cholesterol cholelithiasis. These studies showed excessive secretion of cholesterol in some but not in all patients with gallstones. Further studies will be necessary to determine the overall importance of cholesterol secretion in the development of cholelithiasis.

Cholesterol gallstone formation has been shown to be associated with definite abnormalities in bile lipid composition and in bile salt kinetics. Several investigators have shown that bile from patients with cholesterol cholelithiasis is usually supersaturated with cholesterol. Moreover, the presence of supersaturated bile appears to precede the formation of cholesterol gallstones. There is also general agreement that in patients with cholesterol gallstones characteristic alterations in bile salt kinetics are seen consisting of (1) decreased bile salt pool, (2) increased fractional daily turnover of cholic and chenodeoxycholic acids and (3) normal bile salt synthetic rates. Despite intensive investigation, a basis for the abnormalities in bile salt kinetics and bile composition has not been established. The clinical observation that in patients with bile salt malabsorption secondary to ileal disease there is an increased incidence of cholesterol gallstones has prompted some investigators to propose a defect in ileal reabsorption of bile salts in all patients with cholesterol cholelithiasis. Studies of bile salt absorption in patients with gallstones have yielded conflicting results. Moreover, it is unlikely that defective ileal reabsorption alone would be sufficient to decrease the bile salt pool size because hepatic synthesis would be expected to increase and thus maintain a normal pool.

One possible explanation for the diminished bile salt pool in patients with gallstones is impaired hepatic bile salt synthesis. In support of this concept, *in vitro* studies in patients with cholesterol cholelithiasis showed decreased activity of the rate-limiting enzyme in bile salt synthesis (cholesterol 7-alpha-hydroxalase). However, these studies are difficult to evaluate because it is dangerous to equate the activity of an enzyme *in vitro* with the kinetics of a reaction *in vivo*. Studies of bile salt synthetic rate *in vivo,* by isotope dilution, showed no difference between patients with cholelithiasis and normal subjects. Furthermore, diminished bile salt synthesis alone would not explain increased fractional daily turnover of bile salts, which has been shown to occur in patients with cholesterol gallstones. At present, the most likely explanations for altered bile salt kinetics in patients with gallstones are (1) formation of bile salt derivatives such as sulfates or glucuronides that are not detected by conventional analytic methods, (2) decreased bile salt synthesis *and* decreased intestinal absorption of bile salts owing to a defect in the absorptive surface of the intestines and (3) increased enterohepatic cycling of the bile salt pool leading to increased fractional daily turnover without a concomitant increase in bile salt synthetic rate.

The third possibility needs further explanation. Normally, the bile salt pool is cycled two to three times per meal or six to nine times per 24 hours. Alterations in the rate of enterohepatic cycling would be expected to have profound effects on bile salt kinetics and perhaps also upon bile composition. Therefore, if an initially normal-sized bile salt pool were cycled more frequently, increased bile salt secretion into the intestine would be expected. Assuming no change in the efficiency of bile salt reabsorption, the quantity of bile salts excreted in the feces per 24 hours would increase. In addition, the quantity of bile salt returned to the liver during the same 24-hour period would be increased. There would be no stimulus for the liver to increase bile salt synthesis. Thus increased fecal losses uncompensated by increased synthesis would lead to a diminished bile salt pool. Eventually, a new steady state would be established in which a small pool would be cycled more frequently and lead to several alterations in bile salt kinetics: (1) decreased bile salt pool size, (2) increased fractional daily turnover of bile salts and (3) normal bile salt synthetic rate. These changes in bile salt kinetics could significantly influence bile composition and lead to production of bile that would contain relatively more cholesterol than bile salts and lecithin and thus be more lithogenic.

The evidence for increased bile salt cycling frequency in patients with cholesterol cholelithiasis is at present circumstantial and will require considerably more investigation. Nevertheless, it is interesting to speculate as to what might cause increased enterohepatic cycling. In man, the basic abnormality might be a hypotensive sphincter of Oddi or a hypercontractile gallbladder, either of

which would produce increased frequency of cycling. Moreover, the defect might be as simple as increased emptying of the gallbladder owing to increased frequency of eating. The latter possibility is extremely attractive for it suggests that cholesterol gallstones could be prevented and perhaps treated by revising the patients' dietary habits. After spending ten years of my life studying the physicochemistry of bile, it would be especially distressing to learn that my grandmother was correct when she told me that if I ate too much and too frequently I would get gallstones.

Treatment with Chenodeoxycholic Acid

Based on the data already available, there seems to be little question that oral administration of chenodeoxycholic acid results in complete dissolution of cholesterol gallstones in most patients, usually within 6 to 18 months of therapy. However, it must be emphasized that chenodeoxycholic acid is an experimental drug. The initial studies of the efficacy of this compound were conducted in human subjects without the benefit of prior phase-one toxicity studies in animals. It was assumed that chenodeoxycholic acid was safe because it occurred naturally in man and had been used for many years in a number of cathartics with no known toxicity. Careful monitoring of liver function tests in patients receiving chenodeoxycholic acid showed only transient elevations of serum glutamic oxaloacetic transaminase, which disappeared despite continuation of therapy. Findings on liver biopsies in these patients were not significantly different from those in patients with gallstones who were not receiving chenodeoxycholic acid. Thus the initial studies suggested that chenodeoxycholic acid was an effective and safe compound for the treatment of cholesterol cholelithiasis in man. However, the data from phase-one studies showed that chenodeoxycholic acid, in doses slightly greater than those used in man, produced liver damage in laboratory animals. The reason for this species difference has not yet been firmly established. Moreover, the studies of chenodeoxycholic acid administration in man are fairly recent and do not afford the opportunity to evaluate long-term toxicity. For these reasons, administration of chenodeoxycholic acid in human beings should be carried out only under stringent experimental protocols in which liver function and liver histology are monitored carefully.

Even if chenodeoxycholic acid is proved to be efficacious and safe, the scope of its use in patients with cholelithiasis will be somewhat limited. Gallstone dissolution takes from six months to two years. Therefore, the drug will not be indicated in patients in whom there are severe and recurrent symptoms or in cases in which there are complications such as pancreatitis. It has been shown that gallstones may recur after discontinuation of chenodeoxycholic acid. Therefore, continued therapy will be required in many patients. Given the fact that chenodeoxycholic acid may have to be administered throughout a patient's lifetime and given the potential for long-term toxicity, it is unlikely that young patients with cholelithiasis will be treated with this compound. In addition, the drug should not be administered to women of childbearing age until extensive studies exclude the possibility of teratogenic side effects. The applicability of chenodeoxycholic acid therapy is further limited by the fact that calcified (radiopaque) gallstones are less effectively dissolved than noncalcified (radiolucent) stones.

In the last analysis, chenodeoxycholic acid therapy will be most efficacious in older patients who are relatively asymptomatic and have radiolucent stones. Perhaps the greatest benefit to be obtained from studies of the pathogenesis and treatment of gallstones will be the development of alternate forms of therapy that are safer, more effective and more rapid than chenodeoxycholic acid.

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CASE REPORTS

Refer to: Lawrence EC, Mills J: Bacterial endocarditis mimicking vasculitis with steroid-induced remission. West J Med 124:333-334, Apr 1976

Bacterial Endocarditis Mimicking Vasculitis with Steroid-Induced Remission

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INFECTIVE ENDOCARDITIS AND VASCULITIS may be difficult to differentiate clinically.[1] Although a favorable response to steroid administration is often interpreted as presumptive evidence for vasculitis,[2,3] we recently encountered two patients with documented infective endocarditis who improved clinically with corticosteroid therapy alone.

Reports of Cases

CASE 1. A 78-year-old woman was referred to Moffitt Hospital on April 10, 1971 because of sudden loss of vision in the right eye and an ophthalmologist's diagnosis of temporal arteritis with thrombosis of the retinal artery.

The temperature was 38.8°C (101.8°F), a grade 2/6 mitral regurgitation murmur was heard, but no splenomegaly, splinter hemorrhages, Osler's nodes or Janeway lesions were present. Vision was 20/800 in the right eye and 20/100 in the left. The right retina was pale with extremely thin vessels. Hematocrit reading was 34 percent, leukocyte count was 11,200 per cu mm, erythrocyte sedimentation rate was 50 mm per hour and no abnormalities were found on analysis of the urine. Two blood specimens were drawn for cultures and, because of a presumptive diagnosis of temporal arteritis, therapy with orally given prednisone (60 mg per day) was started. The patient became afebrile and noted improvement in her vision. Findings from a right temporal artery biopsy carried out the day after admission showed no abnormalities. On day five, growth of an organism was noted in one of two blood cultures. Three additional blood specimens were obtained and cultured; all five cultures subsequently grew Streptococcus viridans. Prednisone therapy was discontinued and intravenous administration of penicillin, 12 million units per day, was begun. The patient recovered without complication and is well four years later.

CASE 2. A 50-year-old woman was referred to Moffitt Hospital on February 3, 1975 because of sudden loss of vision in the right eye and a diagnosis of retinal vasculitis. Five months previously, the patient had had fever with a flu-like syndrome and diarrhea. Results of sigmoidoscopy were consistent with ulcerative colitis although contrast studies showed no abnormalities; salicylazosulfapyridine was prescribed and symptoms resolved. Three months before admission, generalized myalgia and a purplish petechial lesion on the right great toe developed. Hematocrit reading was 38 percent, erythrocyte sedimentation rate was 56 mm per hour and on analysis of the urine there were four to eight red blood cells per high power field. Administration of salicylazosulfapyridine was discontinued and therapy with prednisone (40 mg per day given orally) was begun, with symptomatic improvement. Whenever this dosage was reduced, fever, arthralgia, myalgia and migratory tender nodules in the calves, thighs and palms developed. Two days before admission, sudden loss of vision occurred in the right eye, retinal vasculitis was diagnosed by an ophthalmologist and the prednisone dosage was increased to 60 mg per day.

On admission, vital signs were found to be normal; a right homonomous quadrantanopia and a grade 2/6 mitral regurgitation murmur were noted to be present. Roth spots, splinter hemorrhages, Osler's nodes and Janeway lesions were not found. Hematocrit reading was 38 percent, leukocyte count was 15,000 per cu mm, erythrocyte sedimentation rate was 60 mm per hour and findings on analysis of the urine showed two to five red blood cells per high power field. Tests

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Submitted June 4, 1975.

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for fluorescent antinuclear antibody, lupus erythematosus preparation and rheumatoid factor were negative. On an echocardiogram, thickening of the mitral valve was noted. Streptococcus bovis grew in each of six blood cultures and penicillin therapy, 12 million units per day, given intravenously, was started. The dosage of prednisone was rapidly tapered and discontinued. The patient was well after a four week course of penicillin therapy.

Discussion

To our knowledge, this is the first documentation of corticosteroid suppression of the clinical manifestations of subacute bacterial endocarditis. Although corticosteroids have been used before in the successful management of endocarditis, the steroids were administered simultaneously with antibiotics or the diagnosis of endocarditis was suspect[2,4-6] making interpretation of steroid effect extremely difficult. The only instance in which an unequivocal steroid remission occurred was the case reported by Numainville and Scarpellino,[7] although the authors believed that the patient had coexistent rheumatic fever. Both of our patients had definite steroid-induced clinical remissions, one lasting nearly a week and the other lasting three months. Fortunately, findings on cultures of blood specimens—drawn as part of a routine workup for patients with fever—and on careful physical examinations led to the diagnosis of endocarditis in both cases.[8]

It was formerly thought that the peripheral manifestations of infective endocarditis were due to embolic phenomena. It is now appreciated that some of these manifestations, such as glomerulitis and Osler's nodes, are due to immune-complex deposition.[4,9,10] In the presence of an avirulent organism such as Streptococcus viridans, corticosteroid treatment might diminish immune-complex deposition (by decreasing antibody production) or reduce the inflammatory reaction at the site of immune-complex deposition, resulting in apparent clinical improvement despite continued infection.[11-14] We are not aware of any case of endocarditis in which remission of nephritis occurred with steroid therapy. The lack of severe nephritis in case 2 despite a prolonged disease course suggests that steroids might be able to prevent nephritis in these patients, but this remains speculative. The pathogenesis of many types of "autoimmune" vasculitis also involves antigen-antibody complex deposition, and response to steroids frequently occurs in patients with these disorders as well.[15-17]

Before steroid therapy is started in any patient with "vasculitis" (with or without fever), blood specimens should be drawn for culture lest the clinician be falsely reassured by a patient's favorable clinical response to these agents and not recognize the infectious nature of the disease process. When patients have an illness compatible with either vasculitis or "culture-negative" endocarditis (that is, endocarditis due to microorganisms not recoverable with standard blood culture media), the response to antibiotics (such as penicillin and an aminoglycoside) should be tested before starting steroid therapy.[9]

Summary

In two patients with infective endocarditis, a misdiagnosis of vasculitis was made at first and treatment with corticosteroids was begun, resulting in clinical improvement. Some of the manifestations of infective endocarditis are caused by antigen-antibody complex deposition similar to that seen in some "autoimmune" disorders. Therefore, response to corticosteroids cannot be used to differentiate between these two diseases.

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Refer to: Connors MH, Sheikholislam BM: Identical male twins with congenital adrenal hyperplasia—Comparison of growth, serum and urinary steroids. West J Med 124: 335-338, Apr 1976

Identical Male Twins with Congenital Adrenal Hyperplasia

Comparison of Growth, Serum and Urinary Steroids

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THE SALT-LOSING form of congenital adrenal hyperplasia (CAH) results from an inborn error of steroid metabolism that is genetically determined and autosomal recessive.[1] It is known to occur in siblings but to our knowledge there is only one report of this form of the condition reported in identical twins.[2] The effect of the 21-hydroxylase enzyme deficiency in some patients is a lack of cortisol and mineralocorticoid biosynthesis. There is increased adrencorticotropin (ACTH) secretion because of the cortisol deficiency and this can be largely suppressed by exogenous glucocorticoids. Therapy is aimed at suppression of excess ACTH by physiological amounts of glucorticoids to prevent virilization and rapid skeletal maturation. Discontinuation of therapy usually results in a prompt increase in adrenal androgen secretion. The cortisol replacement therapy is adjusted on the basis of the growth pattern and the urinary steroid concentrations. Growth retardation has still resulted in some patients despite application of these principles of therapy. This paper reports the first cases of CAH in identical male twins, which afforded us the opportunity to compare adrenal function as well as growth rates on varying glucocorticoid replacement regimens. The usefulness of plasma 17-hydroxyprogesterone (17-OHP) levels for the diagnosis of CAH and the therapeutic management is compared with the measurement of urinary steroid metabolites.

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Submitted, revised, August 11, 1975.

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ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropin
CAH = congenital adrenal hyperplasia
17-OHP = 17-hydroxyprogesterone
DOC = desoxycorticosterone
GH = growth hormone

Report of Cases

The babies were born after an uneventful 36-week pregnancy. The delivery was normal. The parents are not related and there is no family history of genital abnormalities or deaths in the neonatal period. There are two healthy siblings. The first twin G.S. weighed 4 pounds 11 oz at birth and the second D.S. weighed 4 pounds 7 oz. The placenta and amniotic membranes were not examined. Findings on physical examination were within normal limits and the twins looked alike. Major and minor blood groups were identical. Both twins required oxygen during the initial 48 hours of life because of respiratory distress. At five days of age both twins began regurgitating all feedings and losing weight. D.S. became severely dehydrated and had an episode of respiratory arrest at eight days of age. Serum electrolyte concentrations on the eighth day of life were: for D.S., sodium 126 mEq per liter, potassium 11.3 mEq per liter; for G.S., sodium 121 mEq per liter, potassium 12.1 mEq per liter. Resuscitation was successful and was followed by intravenous infusion of normal saline and hydrocortisone sodium succinate (Solu-Cortef®). Administration of desoxycorticosterone (DOC) acetate, 2 mg per day, was begun by the private physician.

The conditions of infants improved, and at 11 days of age they were transferred to the University of California, Davis-Sacramento Medical Center. A regimen of dexamethasone, 0.9 mg divided into four doses per day, was begun and 24-hour urine specimens were obtained which showed on analysis negligible amounts of 17-ketosteroids and pregnanetriol excretions of 0.1 and 0.3 mg per 24 hours (Table 1). At 12 days of age baseline plasma 17-OHP concentrations, determined by radioimmunoassay method[3] were low in D.S. and elevated in G.S., but in both infants there were abnormally high values 30 minutes after the intramuscular administration of

TABLE 1.—*Effect of Glucocorticoid Therapy on Steroid Metabolites in Identical Male Twins (G.S. and D.S.)*

		Urinary (mg/24 hours)				Plasma 17-OHP (ng/ml)			
		17-ketosteroid		Pregnanetriol		Baseline		Adrenal Stimulation*	
Age	Treatment	G.S.	D.S.	G.S.	D.S.	G.S.	D.S.	G.S.	D.S.
12 days	0.9 mg dexamethasone during 24 hours	0.5	0.7	0.1	0.3	6.13	0.63	8.3	8.3
2 months	2 days after 25 mg cortisone acetate	..	..	1.7	3.5	..	..	..	..
4 months	2 days after 25 mg cortisone acetate	..	..	0.2	..	..	..	..	..
11 months	1 day after 25 mg cortisone acetate	0.6	0.9	0.4	0.5	1.26	4.28	..	..
	2 days after 25 mg cortisone acetate	0.5	1.0	0.5	0.4	1.24	1.24	..	..
	3 days after 25 mg cortisone acetate	0.7	0.6	0.2	..	4.94	4.06	7.21	8.28
16 months	Oral cortisol 10 mg	1.7	1.7	0.4	0.3	..	..	..	..
17 months	Oral cortisol 5 mg	1.3	1.0	1.0	0.6	..	..	..	..
18 months	Oral cortisol 5 mg	1.3	1.0	0.9	1.2	..	..	..	..
	No cortisol × 5 days, daily stimulation*	1.0	1.3	1.1	0.7	..	..	13.7	..
21 months	No cortisol × 5 days	1.7	3.0	6.4	8.8	..	..	..	..

*0.25 mg α 1-24 corticotropin (Cortrosyn®) given intramuscularly; plasma for 17-hydroxyprogesterone (17-OHP) obtained after 30 minutes.

Cortrosyn® (α 1-24 corticotropin). Attempts to gradually reduce the daily DOC acetate administration resulted in urinary sodium loss and increased serum potassium concentrations indicating mineralocorticoid deficiency. Conditions of the twins were stable on a regimen of 25 mg of cortisone acetate given intramuscularly every three days, 1 mg of DOC acetate per day and orally given sodium chloride supplementation. Intravenous pyelograms were interpreted as normal at one month of age with no evidence of adrenal calcification in either patient. At 45 days of age they weighed 5 pounds and were discharged on a regimen of 25 mg of cortisone acetate given intramuscularly every third day, 18.75 mg of DOC trimethylacetate per month and 2 gm of salt daily as a supplement to dietary sodium. The diagnosis at discharge was adrenal insufficiency due to adrenal 21-hydroxylase deficiency.

Vomiting and irritability developed 23 days after the injection of DOC-trimethylacetate and the children were admitted to hospital. The serum electrolyte concentrations were: for G.S., sodium 130 mEq per liter, potassium 8.5 mEq per liter; for D.S., sodium 127 mEq per liter, potassium 10.1 mEq per liter. At this time 24-hour urine specimens showed 1.7 mg of pregnanetriol for G.S. and 3.5 mg for D.S. These values were obtained two days after the last dose of cortisone acetate. Because of these findings the dose of DOC-trimethylacetate was increased to 25 mg per month. The twins did not do well over the next nine months, with repeated episodes of vomiting and irritability occurring 24 to 27 days after each injection of DOC-trimethylacetate. Collections of 24-hour urine specimens repeatedly showed negligible changes in 17-ketosteroid and pregnanetriol levels (Table 1). When the infants were 11 months old, plasma concentrations of 17-OHP were determined at 8 AM on three consecutive days following administration of 25 mg of cortisone acetate (Table 1). Daily fluctuation of 17-OHP levels in the abnormal range was found despite the low urinary excretion of steroids. On the third day after receiving cortisone acetate, 0.25 mg of Cortrosyn was given intramuscularly to each patient at 8 AM and further elevations of the plasma 17-OHP concentrations were found after 30 minutes. At 11 months of age two 125 mg DOC acetate pellets were implanted in each child, and oral administration of cortisol was begun in a dosage of 5 mg three times a day; irritability did not recur.

The growth of the twins continued to be poor (Figure 1) and therefore the total cortisol dosage was decreased to 10 mg per day at 16 months and 5 mg per day at 17 months of age. Despite these reductions there were only slight increases in the urinary levels of 17-ketosteroids and pregnanetriol (Table 1). At 18 months of age the cortisol was discontinued and 0.25 mg of Cortrosyn was administered intramuscularly for five consecutive days in order to determine whether the adrenal hypoactivity was reversible. Urine specimen collections begun on the fifth day showed no measurable increase in 17-hydroxysteroids, 17-ketosteroids or pregnanetriol levels. In contrast, however, the plasma 17-OHP concentration in G.S. at the end of this period had reached a level of 13.7 ng per ml.

The twins' rate of growth now began to increase while being given 5 mg per day of cortisol.

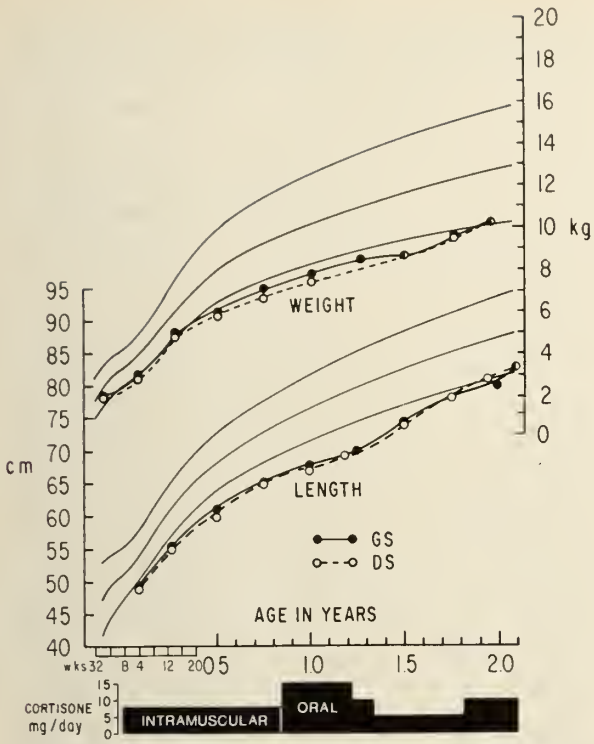

Figure 1.—Comparison of growth of identical male twins (G.S. and D.S.) corrected for gestational age and glucocorticoid dosage. Growth lines represent 2 SD and mean. Chart modified after Tanner.

At 21½ months the administration of cortisol was again discontinued for five days and urine specimens collected at the end of that period. The levels of 17-ketosteroids and pregnanetriol were now abnormally elevated, indicating the return of endogenous adrenal activity.

At 22 months of age both twins began to exhibit irritability and were found to be hyperkalemic and hyponatremic. Administration of 0.1 mg per day of 9α-fluoro-hydrocortisone (Florinef®) was started along with 10 mg per day of cortisol (given orally, half the dose in the morning). They have done well on this replacement regimen.

Discussion

Congenital adrenal hyperplasia resulting from 21-hydroxylase deficiency is not clinically apparent in newborn male infants. In the absence of a positive family history the condition may remain unrecognized until severe dehydration and salt depletion develop. These crises may not occur until after the newborn has gone home from the nursery and thus the cause of death may not be known. Most female infants born with this disorder are usually diagnosed at birth due to apparent virilization. This difficulty in diagnosing the salt losing type of CAH in males probably accounts for the preponderance of females with this disorder in some clinics. Early treatment begun with cortisone and DOC acetate because of the electrolyte abnormalities found during the salt losing crises can be lifesaving but can also delay a definitive diagnosis. These events occurred in the identical male twins described in this report. The dehydration and the salt loss were remarkably similar in timing and severity. Because of their small size and unstable condition we attempted to make the diagnosis of CAH without the discontinuation of steroid therapy. An equivalent amount of dexamethasone was substituted for their cortisone in order to reduce interference with the measurement of endogenous urinary steroid metabolites. The negligible amount of urinary steroid measured was not diagnostic of CAH. Plasma 17-OHP determinations were obtained in order to differentiate CAH from complete adrenal insufficiency.

In normal infants up to six weeks of age, the mean value for plasma 17-OHP is 2.1 ng per ml.[4] In three normal patients stimulated with ACTH, the plasma concentration of 17-OHP ranged from 2.4 to 4.8 ng per ml.[5] Values in most untreated patients with CAH range from 1 to 40 ng per ml.[4] Franks found slightly higher values of plasma 17-OHP in untreated patients with the salt-losing form of CAH.[5] Therefore, plasma concentrations of 17-OHP are usually much higher in untreated patients with CAH than in normal subjects, even normal subjects treated with ACTH. After treatment of CAH with glucocorticoids, the 17-OHP concentration decreases notably and may become normal.[4-6] Utilizing a competitive protein binding method for measurement of 17-OHP, Barnes and Atherden showed there to be an increase after adrenal stimulation in the plasma 17-OHP concentration of children with CAH who were treated with suppressive doses of cortisone.[6] No detectable increase after adrenal stimulation was found in normal children.

In the identical twins in this report resting plasma 17-OHP levels were found to be elevated in only one after the first four days of glucocorticoid therapy. Both twins had an increase in plasma 17-OHP concentration after adrenal stimulation and this along with the salt-losing tendency confirmed the diagnosis of a 21-hydroxylase defect of the adrenal. The genetic expression of the adrenal enzymatic defect was much the same in

both twins, as indicated by the comparable pattern of urinary steroid excretion during therapy. The chief urinary metabolite of 17-OHP is pregnanetriol. While periodic measurements of plasma 17-OHP during therapy showed abnormal concentrations, the urinary pregnanetriol as well as 17-ketosteroid amounts were normal on many occasions. This may be explained in part by the DOC acetate which the twins were receiving. The radioimmunoassay method used to measure 17-OHP also measures DOC with the percent cross-reactivity being 35 percent.[3] This interference, however, would not account for the rapid rise in 17-OHP measured in the plasma 30 minutes after adrenal stimulation. Therefore, measurement of the plasma 17-OHP concentration is of value in the diagnosis of the 21-hydroxylase deficiency form of CAH but as a guide to therapy it may be too sensitive an index of adrenal activity.

In the twins at first there was evidence of subnormal linear growth as well as delayed skeletal maturation which could be due to the steroid they received. Intramuscular injections of 25 mg of cortisone acetate were given every third day as has been recommended for the first year of life.[7] The adrenal hypoactivity and growth retardation which ensued suggest that this dose of glucocorticoid was excessive. The normal cortisol production rate has been determined to be 12.1 ± 2.9 mg per sq meter per day from the age of four months to 20 years.[8] The dose of steroid the twins received represented 20 to 30 mg per sq meter per day during the first year of life. Raiti and Newns[9] found that eight of 35 children with the salt-losing form of CAH who received oral cortisone doses in excess of 36 mg per sq meter per day failed to grow satisfactorily. The intramuscular glucocorticoid dosage used in our patients was well below this limit during the first year of life and still growth was poor. Although cortisone acetate injections every third day have not been shown to suppress growth hormone (GH) release in subjects with CAH,[8,10] the continuous blood level of cortisol maintained under these conditions may interfere with peripheral GH action. Rudman and associates[11] have shown that cortisol given near the time of GH administration diminishes the peripheral anabolic actions of GH. The daily oral dose of cortisol usually recommended is twice the cortisol production rate.[12] In these patients oral cortisol therapy was started at 11 months of age and amounted to 37 mg per sq meter per day but this was decreased to 10 mg per sq meter per day at 17 months. It was around 18 months of age that catch-up growth occurred. The growth retarding effects of steroid therapy seem related not only to dosage, but also to the hormone preparation.[13]

It appears from our analysis of growth in these identical twins that relatively low doses of glucocorticoids were required to suppress both steroid excretion and growth. Identical increases in growth rate occurred along with adrenal suppression with the oral cortisol dose of 10 mg per sq meter per day. The similarity of responses in these twins with identical genetic makeup supports the concept that certain patients with CAH may be treated successfully with less than the usual recommended glucocorticoid therapy. In contrast to measurements of plasma 17-OHP levels and urinary steroid metabolites the linear growth rate of these patients was found most reliable in the therapeutic management.

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LETTERS *to the Editor*

Metronidazole for Trichomonas Infections

To the Editor: I read with great interest the article entitled "Infectious Urethritis in Men and Women" by Dr. Edwin M. Meares, Jr., in the December 1975 issue of The Western Journal of Medicine (123:436-441, Dec 1975).

In particular I make reference to the treatment regimen for trichomonas urethritis in which Dr. Meares does not suggest an alternate other than metronidazole in the management of that disease. In a letter dated October 27, 1974 to the Commissioner of Food and Drug Administration by the Health Research Group of Washington, D.C., they urged the FDA to take prompt action against the use of metronidazole because of its potential as a carcinogenic agent in rodents and mutagenic in bacteria. In addition the medical letter of June 1975 states, "It should not be used, i.e., metronidazole, for trichomonas infections that can be made asymptomatic by other means." This is rather strong language and as an internist I would like to know from Dr. Meares if there is an effective alternate form of treating both sexual partners who have trichomonas urethritis.

Leonard S. Grabowski, MD
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* * *

The Author Replies

I welcome the opportunity of responding to Dr. Grabowski's letter and his questions regarding the use of metronidazole (Flagyl®) for the treatment of genitourinary tract infections in men and women due to Trichomonas vaginalis. Many physicians are aware of the studies conducted in laboratory animals that have shown a carcinogenic potential of metronidazole in those animals that were studied. Many physicians are also aware of the recommendation that was made by the Health Research Group of Washington, D.C., to the United States Food and Drug Administration (FDA) in petitions dated March 20, 1974 and October 22, 1974 that metronidazole be withdrawn as an approved agent in the treatment of trichomonal vaginitis. Unfortunately, to my knowledge, the results of the hearings and extensive research that were conducted by the Food and Drug Administration regarding the use of metronidazole in human patients have never been published in any journal or news media that has been readily available to the medical profession.

On October 21, 1975 Dr. Alexander M. Schmidt, Commissioner of the FDA, forwarded to the Health Research Group of Washington, D.C., the results and conclusions of the FDA's investigations regarding the use of metronidazole. Under the Freedom of Information Act, this document is public property and can be freely quoted without special permission. In fact, I have been informed by the FDA that copies of this letter have been sent out extensively to members of the medical profession who have made inquiries regarding this matter and that the FDA plans to send out a printed summary of this letter to various members of the medical profession in this country in the near future.

At this time Dr. Grabowski's questions can best be answered by the following direct quote from the conclusions made in the letter cited above by Dr. Alexander Schmidt to the Health Research Group of Washington, D.C.:

"The FDA shares your concern over the carcinogenicity of metronidazole in rodents. Nevertheless, the available evidence indicates that the total dose of metronidazole given to patients is of such low order of magnitude when compared to the life-span doses given to rodents, that the element of carcinogenic risk in treating trichomoniasis is very low.

"Further, it is our conclusion, which is shared by many experts and by our OB-GYN Advisory Committee, that Trichomonas vaginitis is an important disease causing much suffering among its victims, and that metronidazole is the only drug currently marketed in this country which is effective in its cure.

"We therefore conclude that benefits-risk considerations at this time indicate that metronidazole should continue to be available for the treatment of trichomoniasis, with labeling which includes an adequate discussion of animal carcinogenicity and possible carcinogenic hazard to humans and provides guidance on appropriate uses of the drug. The labeling is currently undergoing revision with

respect to the indications and warnings section, and a box warning is being developed.

"Finally, we believe it will prove possible to reduce the amount of nitroimidazole used in treatment. Studies of a single-dose regimen of tinidazole will therefore be permitted to proceed. Further, the effectiveness of shorter courses of metronidazole, at lower doses, which are used in Europe, is currently being evaluated."

Regarding the question of mutagenicity, Dr. Schmidt stated: "Mutagenicity testing is a very important new area of drug evaluation. At the present time, however, it is premature to use the results of such testing to draw conclusions regarding the safety of drugs for human use. This is particularly true for mutagenicity testing in submammalian systems. Regarding our present ability to interpret mutagenicity data obtained in microbial testing systems, Dr. Samuel S. Epstein said: '. . . the presumptive relevance of such data to man is highly questionable. . . .There is an enormous range of differences in the body chemistry, metabolism, et cetera, that make it untenable to extrapolate directly from nonmammalian systems to mammalian systems using *in vivo* methods.' (Testimony before the Senate Subcommittee on Executive Reorganization and Government Research, April 6, 1971.)"

It is hoped that this information will clarify the points raised by Dr. Grabowski—both for him and for readers of the JOURNAL.

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Ampicillin Resistant Hemophilus Influenzae Type B in the West

TO THE EDITOR: In March 1974, the first report of meningitis caused by ampicillin resistant hemophilus influenzae type B was published from the Center for Disease Control.[1] Sensitivity studies revealed that on ampicillin disk testing, these organisms had less than an 8 mm clear zone, whereas sensitive strains had greater than a 20 mm clear zone, and on tube dilution studies these organisms had greater than 8 μg per ml minimum inhibitory concentration, whereas sensitive strains have less than 2 μg per ml minimum inhibitory concentration.

Previously, there had been case reports of failure of ampicillin to eradicate H. influenzae type B but on examination it was found that no cases of drug-resistant strains were validated, but rather inadequate dosage, inappropriate route of administration or compromised host defense was found.

Since the report in March 1974, many case reports of ampicillin resistant Hemophilus influenzae type B infections have been published from the eastern United States. This development of resistance was associated with production of beta-lactamase, the presence of which can be bioassayed. In Atlanta in July 1974, out of 25 isolates from blood or cerebrospinal fluid (CSF), 16 were found resistant to ampicillin and found to require a minimum bactericidal concentration greater than 12 μg per ml, whereas it is known that CSF levels greater than 5 μg per ml are difficult to obtain.[2] In a report from Washington, DC, 10 percent of isolates during the first half of 1974 were found beta-lactamase positive and ampicillin resistant.[3]

In Denver in 1974, a report of 83 children with Hemophilus influenzae infections at three pediatric hospitals showed no resistant organisms,[4] and not until the spring of 1975 were there reports from Denver, at the Society for Pediatric Research Meetings, that a resistant organism was isolated from children with disease.

In Los Angeles, surveillance of *in vitro* susceptibility of isolated strains to ampicillin and chloramphenicol immediately commenced, after publication of these reports of resistant Hemophilus influenzae type B, and results were compared with those of sensitivity studies of isolates obtained a decade earlier.[5] All isolates from 1974 were beta-lactamase negative and uniformly were sensitive to both antibiotics. However, after submission of their article in 1975, these same workers obtained an isolate from a child with meningitis treated in Pasadena who was resistant to ampicillin and produced beta-lactamase.

In San Francisco, since these reports were noted in 1974, surveillance of Hemophilus influenzae type B has been carried out at Children's Hospital of San Francisco (with bacteriology studies done by Dr. Wie-Shing Lee), and no cases of meningitis or septicemia due to beta-lactamase producing ampicillin resistant organism were noted from January 1974 to October 1975.

In October 1975, an 18-month-old boy developed septicemia, pneumonia and empyema from which Hemophilus influenzae type B were

obtained from blood, throat and empyema fluid. This organism was found to produce beta-lactamase and to have a minimal inhibitory concentration of 16 μg per ml and a disk zone size of only 6 mm as confirmed by the Center for Disease Control. This child was treated initially with ampicillin and when the isolates were found to produce beta-lactamase, he was switched to chloramphenicol on which he subsequently made a good recovery.

In January 1976, a 10-month-old child presented with meningitis, and Hemophilus influenzae type B were isolated from his CSF. He was started on ampicillin and chloramphenicol and 24 hours later the isolates were found to produce beta-lactamase. Administration of ampicillin was discontinued and he subsequently made a complete recovery on chloramphenicol therapy.

These cases document that resistant Hemophilus influenzae type B organisms are now present throughout the United States, and based on experience in the eastern United States, it can now be expected that in the western United States, 10 to 50 percent of organisms isolated and studied may prove to be ampicillin resistant.

It is now mandatory that all children treated for critical infections—such as meningitis, septicemia, epiglottitis, severe pneumonia with empyema, pericarditis or osteomyelitis from which Hemophilus influenzae type B organisms may be obtained—should be treated with appropriate doses of ampicillin and chloramphenicol from onset and that subsequent drug therapy be based on assays for beta-lactamase production or minimal inhibitory concentration determinations. If the organism is not a beta-lactamase producer, administration of ampicillin alone should be continued. If the organism produces beta-lactamase or demonstrates elevated minimal inhibitory concentration requirements of ampicillin, then chloramphenicol alone should be utilized for therapy.

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Excluding Anesthesiologists

TO THE EDITOR: I have carefully read the article of Jones and Hamburger which recently appeared in THE WESTERN JOURNAL OF MEDICINE (Jones MW, Hamburger B: A survey of physician participation in and dissatisfaction with the Medi-Cal program. West J Med 124:75-83, Jan 1976) and feel very strongly that their exclusion of the anesthesiologists (along with the radiologists and pathologists) does a tremendous disservice so far as the intent of the survey is concerned as well as the potential good that might result from such data in remedial efforts that might be possible by state authorities who control this program (Medi-Cal). It is, in my opinion, rather arbitrary or capricious to exclude anesthesiologists " . . . since they are generally unable to make an independent decision about whom they treat." Certainly the phenomenon that occurred in May 1975 in California should be sufficient grounds to refute the validity of that statement. More important, however, is that the impact that such a small but vital group of health care providers, such as anesthesiologists, has upon the entire health care administered to the Medi-Cal patients should escape their attention or be deemed unworthy of study or evaluation. Bluntly stated, their refusal to participate in all anesthesia services because of the extraordinary medical liability premiums demanded of this small group when coupled with inadequate reimbursement from all state and federally mandated programs precipitated the "crisis" that Governor Brown said didn't exist and yet forced him to call a special session of the California Legislature.

It must also be pointed out that their subsample group of approximately 250 members of the California Medical Association, while perhaps statistically valid for their purposes, excluded any representation from a group of 1,600 anesthesiologists of the California Society of Anesthesiologists who comprise one of the largest single component specialties of the California Medical Association. And contrary to the opinion of some,

these anesthesiologists are, in the main, self-employed health care providers who are not agents of the hospital where they work and bill on a fee-for-service basis just like all other physicians. It is also rather unfair to group anesthesiologists along with radiologists and pathologists whose mode of practice is not even remotely similar. Many, if not most, anesthesiologists provide their own equipment, maintain separate billing offices from the hospital and differ only slightly from their surgical colleagues who also "do their thing" within the hospitals (but without being asked to provide any of the necessary equipment for the practice of their specialty). There is, however, a most significant difference between all members of the surgical specialties and the anesthesiologists, and that is the grossly inadequate reimbursement levels for their respective services.

For reasons that I am not in the least critical of, their survey dealt only with one of the many state mandated programs. But the full impact of the problem—especially as it applies to the anesthesiologists—can not be appreciated unless it is brought out that there are many other programs (both state and federal) which reimburse the anesthesiologists at far less than usual and customary fees, and that they have had and will continue to have a most deleterious effect upon the viability of this specialty. I am referring to the Crippled Children Services, industrial accident cases, Medicare, CHAMPUS, etc. Anyone who is familiar with these reimbursement schedules knows whereof I speak and I do not choose to embarrass my surgical colleagues by listing some of these gross inequities of reimbursement. But they do exist and this fact is well known by the hospital administrators as well as the surgeons.

Surveys as recent as December 1975 indicate that perhaps as many as 25 to 30 percent of the anesthesiological work force have already left the state of California, have entered the military or Veterans Administration hospital systems or are being forced to retire from practice.[1] Similar surveys of the residents-in-training in the field of anesthesiology who are about to complete their training have indicated that they will not practice in California.[2] What is needed is a total reevaluation of the reimbursement schedules for all these state and federally mandated programs as it applies to all specialties—both surgical and nonsurgical. In my opinion, the survey by Jones and Hamburger does a disservice in not pointing out these facts as well as excluding certain specialties which are vitally affected. Neglectful inaction in this area will soon enough result in the destruction of an entire discipline of medicine in the very near future and will have a profound and disruptive effect upon the quality and quantity of health care to all Californians—and just maybe everyone in the United States.

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The Authors Reply

IN RESPONSE to Doctor Lauber's letter, the following details will explain the exclusion of anesthesiologists from the results of the Medi-Cal Participation Survey.

A total of 48 out of 72 anesthesiologists randomly included in the sample returned their questionnaires. Among these respondents, 18 merely commented that their own situation was not applicable to this survey, since they do not choose whether or not to accept Medi-Cal patients for treatment. Of the 30 who did complete at least a portion of the questionnaire, several indicated that they were answering the questions hypothetically. This response was similar for pathologists and radiologists.

In summary, more than one third of respondents in these specialties disqualified themselves in this manner and virtually all others indicated that they treat *all* patients referred to them (many noting that they have little or no choice in the matter). While sharing Doctor Lauber's concerns, the authors nevertheless concluded that data from anesthesiologists were not specifically relevant to the issues being studied. Such responses, furthermore, would have distorted the overall survey results.

As with other physicians, many anesthesiologists who did respond indicated dissatisfaction with the Medi-Cal program, and several cited problems with reimbursement far below their usual fees.

MICHAEL W. JONES, MBA
BETTE HAMBURGER, BA

Quality of Life

To the Editor: The January issue of your journal carried the editorial question: "But what is meant by the quality of life?" (Quality of life—A new national purpose? West J Med 124:55-56, Jan 1976); and further asked " . . . what might be the role of medicine (?)"

Although the article covered a wide range of desirable human needs, the role of the physician should be in disease prevention. As a pathologist I find it difficult to imagine "quality of life" without longevity and freedom from disease. While working with the local Medical Examiner, I performed many autopsies. I considered two thirds of the deaths "preventable" since they were clearly related to life-style ("loafer's heart," "smoker's lung" and "drinker's liver"). Our high standard of living contributes to this. Populations that have been virtually free from these problems include those peoples who live close to the Stone Age level of existence (Masai warriors[1] and the Tarahumara Indians[2]); or in remote mountain villages where Western luxuries are rare (Hunza[3]). I advocate the life-style of the marathon runner and monitor autopsies on distance runners in an effort to bring the longevity of the Hunza into our modern cities.[4] Thus far, I have found no reports of deaths due to any of the above three "preventable" diseases among those who have covered 42 km on foot at any time in their life. This is in spite of the fact that many of the hobby runners were former loafers, smokers and drinkers!

The marathon life-style includes:

- Mileage (ten kilometers a day on foot),
- Moderation (no tobacco and scant alcohol),
- Macrobiotic diet (little refined foods).

The first duty of a physician is to set a good example so that his patients might follow it and avoid diseases. His second duty is to assist those with established disease so they may enter the life-style safely. Rehabilitation programs aiming at the distance run can be rewarding. I have just returned from the "Primo 50 Mile Fun Run" supported by the rehabilitation program of the Honolulu Y.M.C.A. Eleven former cardiac patients, "graduates" of that program, took part in the noncompetitive event and performed as well as the nonpatients. Covering fifty miles on foot may sound like an impossible task for elderly persons who have started to show symptoms of atherosclerosis, but I believe that it clearly shows the benefits of the marathoner's life style; and there is no question that such a capability would improve the *Quality of Life* of anyone.

The age range of the patients in the Primo-50 was 41 to 64. Most had been training under their cardiologist-coach for less than two years, a very small time investment for such a large reward of fitness!

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Editor's Note: Medicine and Quality of Life will be the subject of a future Special Issue of The Western Journal of Medicine.

Refer to: Robertson WO: Medical library services—Innovations in Washington (In the Forefront). West J Med 124: 344-345, Apr 1976

Medical Library Services

Innovations in Washington

WILLIAM O. ROBERTSON, MD, *Seattle*

AT THE CLOSE of the last century, Seattle's physicians, recognizing both their geographic isolation and the absence of scholarly resources (books and journals), founded the area's first medical library. Almost immediately they also founded a medical journal, *Northwest Medicine,* which was to serve as the official state medical journal for Washington, Oregon and Idaho during the next half century. Not the least of the journal's goals was that of attracting journals and new books to the newly founded library at no cost through its book review section and its reciprocal complimentary subscription program.

As hoped, the library, the journal—and the region—grew and prospered. Eventually, the more than 25,000 volume library was brought under the jurisdiction of Seattle's King County Medical Society (KCMS). Located in a large office building in the center of the downtown community, it shared space with the medical society offices. It proved ideally accessible to many specialists in the building and in the immediate neighborhood.

But times change. The area burgeoned; physicians migrated to the suburbs. Suddenly, in 1971, the rent for the library space soared from $1 a year to $2,000 a month—making the rental budget larger than the library's total operational budget. Fortunately, discussions had already been held about alternatives for the library's long-range future. Several of the community's larger hospitals had been building commendable collections and the University of Washington's Health Sciences Library had emerged on the scene as an active coordinating, collaborating resource to the region's health practitioners. But nothing really happened until the rent went up. At that point the King County Medical Society's library committee and its Board of Trustees began vigorous discussions with the University of Washington about still further collaboration; these culminated successfully in February 1971 when KCMS—first transferring some of its unique references to the University of Washington—put its library holdings in storage. Simultaneously, KCMS entered into a contractual arrangement with the University and stationed its librarian on the University premises. Using a special telephone and the University's collection, and with access to photocopy capability, the librarian services the membership's library needs. She completes MEDLINE, SDILINE, TOXLINE and other National Library of Medicine bibliographic searches, photocopies articles and handles other reference requests.

During the ensuing three years more than half of the Society's membership availed themselves of the new service—at a rate five times that of previous usage. By careful attention to effective and efficient service, the librarian has drawn accolades; and the cost of the program continues at $15 per member per year. To help plan for the future, the librarian, Ms. Barber, using simple postcards, has conducted a continuing survey of the members' opinions about the service and the use to which they are putting it in their individual practices. Results of the latest tally (March 1974 to March 1975) show more than 65 percent of the requests stem from patient care problems; the remainder have to do with continuing education needs, research activities, public information programs and so forth. Moreover, more than 95 percent of the respondents indicate the service has satisfied their specific needs and always within a reasonable time span.

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Elsewhere in Washington, Spokane's physicians also founded a medical library early in this century. Lacking any formal health education institutions, the Spokane Medical Library, founded in 1929, and the Sacred Heart Hospital Library have provided the backbone of services for the "Inland Empire." Similarly, physicians in Tacoma developed their own library in 1967. Recently, they took the lead in "regionalizing" their resources by jointly employing a librarian on behalf of their medical society and several hospitals. She maintains the county society's collection along with Tacoma General Hospital's collection in one location and oversees the other community hospitals' collections, assuring maximum access and efficiency to the members.[1]

With the emergence on the national scene of "*Your* National Library of Medicine"[2] and the development of our five-state Pacific Northwest Regional Health Sciences Library, it became even more obvious that although physicians in our three urban areas enjoyed excellent library services, those located elsewhere in the State were "disadvantagd." To respond to that need, the Washington State Medical Association (WSMA), in cooperation with the University of Washington, initiated a statewide service available to all of its members regardless of geographic location. Today, any member physician can write or simply telephone on a toll-free telephone line to submit a request. The WSMA librarian, also stationed at the University of Washington's Health Sciences Library, responds quickly to the call with a full range of services.

The WSMA's program has been underway for barely four months; its reception has been most favorable. Its second month generated more than 200 requests—over and above those requests serviced directly by the three larger county society programs. At the end of four months the service had provided WSMA members with more than 310 searches and photocopied more than 1,500 articles—again in addition to the local society activities. Our goal is to seek maximum cost benefit on the local scene; operationally this is what is occurring. Simultaneously we are investigating how an individual physician (or groups of physicians) can best integrate this service into his current practice so as to respond to his continuing education needs. For our first year, the program is being conducted on a budget of less than $30,000 —less than $8 per member per year. At present future funding alternatives—adding a service fee plus participation by community hospitals—are under study. WSMA's goal is to combine our individual member's dollars with those of larger institutions and organizations *and* with tax dollars to maximize access to up-to-date knowledge for each and every physician in the state. The potential for enhanced learning and improved patient care is enormous—all at minimal cost and located in the physician's own community.

A spin-off of this program has brought medical library services to our sister state of Montana and its higher education system. The collection of the King County Medical Society's library that was originally put in storage has now been sold via the assistance of the Washington/Alaska Regional Medical Program to Montana State University in Bozeman at a relatively low cost. Once the books were on hand, Montana State University was able to accrue $50,000 of support from the State of Montana and $50,000 of support from the federal government to build a Health Sciences Library as part of Montana State University—which eventually will service the needs of health care providers throughout that state.

Little doubt exists that the "networking" of health information services will become more and more crucial to all health care providers throughout our region. Certainly, most physicians ought to be able to satisfy their information needs with local resources; this is mandatory—but no community is able to be 100 percent independent in our one "world of medicine." Sharing of information resources is the road to the future. A combination of resources now serves to provide for better services than were available a scant decade ago. Still additional dollar resources will be needed to maintain the system. Obviously, the basic elements of the system are likely to continue to be supported by existing resources, but many involved foresee charging individual users on a minimal "fee-for-service" to create the greatest possible efficiency and effectiveness for the system. In addition to supporting the network, such arrangement would assure users some control of the overall process. The physicians in the State of Washington have assumed the leadership in bringing this evolutionary program about; we would encourage others to consider the approach.

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The National Library of Medicine

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WILLIAM H. WELCH, one of the towering figures in American medicine, declared that there were four major medical contributions of the United States in the 19th century: the development of anesthetics, the discovery of insect transmission of disease, the establishment of the modern public health laboratory and the development of the Library of the Surgeon-General's Office (Army) and the *Index-Catalogue* of that collection. Of the four, Welch believed the last was the greatest.[1]

The legacy of that accomplishment is an institution in which American physicians today can take justifiable pride: the National Library of Medicine (NLM). The Library (Figure 1), now a part of the National Institutes of Health in Bethesda, Maryland, is the lineal descendant of the Library of the Surgeon-General's Office.

The Billings Era

Although the Library dates its founding from 1836, it was not until John Shaw Billings, an Army surgeon, assumed charge in 1865 that the Library began to be regarded as a medical treasure of the first order. Under Billings' direction, the collection grew from 1,800 volumes (1865) to 117,000 books and 192,000 pamphlets at the time of his retirement in 1895.

Billings' tireless efforts to collect all of the world's growing body of medical literature can be traced to his experience as a medical student. In attempting to write a dissertation he discovered that there was no library in the United States, public or private, where a medical practitioner or researcher might find a large body of the published literature relating to any medical subject. Thus it was, when the position was offered to him, he eagerly accepted the responsibility of directing the Library of the Surgeon-General's Office.

In 1879 Dr. Billings developed a guide to the world's biomedical journal literature which is today, almost one hundred years later, familiar to medical professionals—*Index Medicus*. Billings' greatest achievement, however, was the publication, beginning in 1880, of the *Index-Catalogue of the Library of the Surgeon-General's Office*. This covered all of the world's published literature, journal and monograph, in the Library's collection, organized by subject and author. It was to take 15 years for the entire 16-volume catalog to be published, through the letter Z. Now, for the first time, any medical student writing a dissertation here or abroad had under firm control the bulk of the literature that he needed.[2]

To this day, descendants of the two works (the former still under its original title, the *Index-Catalogue* now superseded by the *NLM Current Catalog)* continue to be published by the National Library of Medicine. Whether Billings' comment on all this indexed and cataloged material also continues to be valid is left to the reader: "The proportion of what is both new and true is not much greater in medicine than it is in theology."[2]

Dr. Billings, in addition to his duties at the Library, was in charge of vital statistics for the Tenth Census (1880). He discussed with Herman Hollerith, a young engineer in the Census Office, the need for a machine to do the purely mechanical work of tabulating the census and population

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Figure 1.—The National Library of Medicine is on the grounds of the National Institutes of Health in Bethesda, Maryland.

statistics. Billings suggested that statistical data might be recorded on a card by punching small holes in it and that these cards might be counted and sorted mechanically.[3]

As Hollerith later wrote, "After studying the problem I went back to Dr. Billings and said I thought I could work out a solution for the problem and asked him would he go in with me. The Dr. said no he was not interested any further than to see some solution to the problem worked out."[4]

Hollerith did indeed work out a solution to the problem, and the first electric tabulator he developed, based on the principles Billings suggested, was used with great success in the 1890 census. With his equipment, the classification and counting were done in a third the time of the 1880 census. Hollerith subsequently improved and refined his machine and eventually sold his patents to what is now IBM.

MEDLARS

These two accomplishments—an index to the medical literature and a rudimentary computer—evolved independently down through the years. Then, in the 1960's, they were brought together in a way that even Dr. Billings could not have foreseen. The result of this union was MEDLARS, the computer-based Medical Literature Analysis and Retrieval System, which became operational at the National Library of Medicine in 1964.

MEDLARS is based on the skilled indexing and cataloging of published materials received by NLM. This aspect of the system—extracting pertinent data from the printed page—would be quite familiar to Billings and, in fact, is essentially similar to the abstracting and indexing he accomplished for the *Index-Catalogue* and the original *Index Medicus*. However, with MEDLARS it now became possible to join this intellectual process with a sophisticated electronic computer for the storage and retrieval of medical information. Using the system, the Library can produce in a matter of hours typeset copy for a 1,000-page bibliography containing more than 20,000 articles indexed each month.

The problem of redundancy and poor quality medical literature, which plagued Billings 100 years ago, is still with us today. The Library entrusts the very important task of selecting journals to be indexed to an advisory group of consultants that includes physicians, editors and librarians. Of the 20,000 health-related periodicals received by the Library, 2,300 are chosen for indexing (including THE WESTERN JOURNAL OF MEDICINE). Even with this high degree of selectivity, the number of journal article citations added each year to MEDLARS approaches a quarter million, and the total is now well over two million.

MEDLARS made possible not only the rapid production of bibliographies but also allowed for searching the data base in response to an inquiry from a health professional. Such individualized searches, however, were slow and required coding by a trained search analyst before being fed into the computer.

Spurred by increasing demands for search services and a growing backlog of requests, NLM undertook in the late 1960's to develop a more rapid and widely accessible system. The result, after several years of experimentation, was the implementation of MEDLINE (MEDLARS On-Line), a new service begun in October 1971.

Using MEDLINE, it is possible for health professionals throughout the United States (and in several foreign countries) to have immediate access to a data base of about half a million citations to the most recent articles. These articles are from more than 3,000 different biomedical journals, including those indexed for *Index Medicus*. Access is through computer terminals that are linked to the National Library of Medicine's IBM 370/158 computers by telephone and other communication lines (Figure 2). More than 300 hospitals, medical schools and medical research institutions in the United States have access to MEDLINE, and more than 400,000 computer searches are made each year.

MEDLINE is an interactive system, that is, the user identifies the journal article references he needs by carrying on a dialog with the computer —typing in successive queries on the terminal keyboard. MEDLINE recognizes some 13,000 medical subject headings, from ABATTOIRS to ZYMOSAN, that may be combined to search on

Figure 2.—Two IBM 370/158 computers are used to prepare the bibliographies and catalogs published by the Library and also provide rapid access to journal article references via MEDLINE.

a specific subject. Users may also search by an author's name, a word in the title or abstract of an article, a publication date, language, a specific journal title or a combination of these elements.

After pertinent references are located, the user prints out at the terminal the author, title, and journal source for each citation. It is also possible in some cases to print out an English abstract of the article. If a large number of references are retrieved (more than 25), they may be printed overnight at the National Library of Medicine and mailed to the requester the next day. The entire on-line search usually takes less than 15 minutes, and the charge is $8.50 or less. Some MEDLINE Centers absorb the costs and make no charge to the user.

MEDLINE services are coordinated by eleven Regional Medical Libraries, each responsible for a geographic area of the country. The Pacific Northwest Regional Health Sciences Library, located at the University of Washington in Seattle, covers the states of Alaska, Idaho, Montana, Oregon and Washington. There are nine institutions offering MEDLINE services in this region. The Pacific Southwest Regional Medical Library Service is centered at the University of California, Los Angeles, Center for the Health Sciences. There are 58 MEDLINE centers in this four-state region (covering Arizona, California, Hawaii and Nevada).

From Citation to "Hard Copy"

To identify the needed literature is just the first step. The long-term trend of an increasing number of journals combined with the recent phenomenon of decreasing library budgets for acquisition make it unlikely that a health professional will be able to locate in a single library all the journal articles identified in a thorough MEDLINE search. Outside of the National Library of Medicine, no other medical library in the United States subscribes to all 3,000 journals in MEDLINE.

To ensure that American physicians have access to this literature, the Library participates in a nationwide interlibrary loan network. If unable to provide a patron with a book or journal from its own collection, a local medical library will send a request for a photocopy to another library in the same region, or to the particular Regional Medical Library. The National Library of Medicine backs up the entire system and attempts to supply photocopies of material unavailable elsewhere.

In order to fill this role as a "library's library," NLM collects a wide range of materials in some 40 biomedical areas and, to a lesser degree, in such related subjects as general chemistry, physics, zoology, botany, psychology, instrumentation and other areas that are peripheral to (but sometimes indispensable in the study of) biomedicine. The holdings include some 1½ million books, journals, technical reports, theses, pamphlets, microfilms, and pictorial and audiovisual materials. More than 70 languages are represented in the collection.

Also housed at NLM is one of the world's finest collections of historical materials relating to medicine, dating from the 11th to the mid-19th century. A room with special temperature and humidity controls preserves the most valuable manuscripts and incunabula (books printed before 1500).

New Programs

In the last decade, the Library's mission has been expanded to include programs of grant support, research and development in the application of modern communications technology, toxicology information and audiovisual collection and development.

The United States Congress, responding to a series of reports and witnesses warning that the nation's medical libraries were in a serious state of disrepair, enacted the Medical Library Assistance Act in 1965. The Act, renewed with changes several times since then, provided for grant assistance for library construction, training in medical library science, carrying out research in library science and communications, improving library resources, establishing Regional Medical Libraries, and supporting publications. To date, almost

$75 million has been distributed by NLM to medical libraries ranging in size from small hospital collections to major medical school libraries.

The second of the new mandates, the application of new technology, is the function of the Lister Hill National Center for Biomedical Communications. Established within the NLM in 1968, the Center is named after one of the cosponsors of the 1956 legislation that transferred the Library from the military to the Department of Health, Education, and Welfare. The Lister Hill Center has pioneered in the application of space-age technology for experimental networks, such as radio and television communication via satellite linking remote Alaska villages with a Public Health Service physician, and a two-way microwave television network in New England tying outlying local health facilities with Dartmouth College.

The third new activity at the Library, the Toxicology Information Program, is responsible for building computer-based data banks of information from the literature of pharmacology/toxicology, environmental pollution, occupational safety and health, and related disciplines. A major accomplishment of this program is the development of the on-line system TOXLINE—Toxicology Information On-Line. Similar in some respects to MEDLINE, the TOXLINE data base makes available to its more than 150 subscribers some 350,000 citations and abstracts to the literature of toxicology.

The National Medical Audiovisual Center, located in Atlanta, Georgia, is another component of NLM with a function not traditionally associated with a library. Audiovisuals are being used with increasing frequency at all levels of health-science instruction—for undergraduate and graduate training, and for continuing education of practitioners.

One of the problems faced by medical educators is that of identifying and acquiring audiovisual teaching materials appropriate for their students. To help meet this need, the National Medical Audiovisual Center has developed a computerized data base known as AVLINE (for Audiovisuals On-Line), accessed by the same terminals as MEDLINE. AVLINE citations contain not only an abstract, but information on where and how the audiovisual material may be obtained, the intended audience, and whether it has been rated "recommended" or "highly recommended" by professional organizations evaluating the material.

Just as NLM provides photocopies of journal articles on interlibrary loan, the National Medical Audiovisual Center lends motion pictures and videotapes to institutions and to individual health professionals. In the past year the Center has filled about 60,000 requests for audiovisual material.

NLM is probably best known in the medical world for the printed bibliographic tools that provide access to this collection—chief among them, of course, being *Index Medicus*.

In addition to *Index Medicus*, however, there are a number of publications of more immediate interest to physicians. *Abridged Index Medicus* for example, is much less expensive and handier for office reference. Each monthly issue lists references to articles appearing in 100 English-language journals selected for their usefulness to the practitioner and for their coverage of all major fields of clinical medicine. Periodical lists of references in a number of medical specialties are prepared by the Library and published by cooperating professional societies and other government agencies. Such disparate fields as cerebrovascular disease, rheumatology, artificial kidney, anesthesiology, neurosurgery, dermatology and hypertension, to name just a few of the subjects, have specialized bibliographies devoted to them.

Despite the Library's involvement with telecommunications, satellites, audiovisuals and computer networks, great emphasis is placed on continuing the proud tradition started in the last century—the acquiring, organizing and maintaining of the world's greatest collection of published health-related literature. The information generated by modern biomedical research, however, has placed an enormous responsibility on the National Library of Medicine to devise improved methods of knowledge transfer. John Shaw Billings would no doubt take the Library's new programs and techniques in stride—viewing them as no more than natural extensions of what he had begun.

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4. Muirhead JF: Doctors afield—John Shaw Billings: Quotation from letter of August 7, 1919. N Engl J Med 268:778-779, 1963

in memoriam

ADAMS, WILLIAM LANIER, JR., Fresno. Died February 2, 1976, aged 66. Graduate of the University of Southern California School of Medicine, Los Angeles, 1934. Licensed in California in 1934. Dr. Adams was a member of the Fresno-Madera Medical Society.

BAUER, FRANZ K., Los Angeles. Died February 10, 1976 in Westwood of heart disease, aged 59. Graduate of Louisiana State University School of Medicine, New Orleans, 1941. Licensed in California in 1944. Dr. Bauer was a member of the Los Angeles County Medical Association.

BERRYMAN, J. SLOAN, Los Angeles. Died January 22, 1976 in Santa Monica of bronchial pneumonia, aged 55. Graduate of the University of Michigan Medical School, Ann Arbor, 1944. Licensed in California in 1945. Dr. Berryman was a member of the Los Angeles County Medical Association.

BROEMSER, MILTON A., Monterey. Died February 9, 1976, aged 86. Graduate of Washington University School of Medicine, St. Louis, 1911. Licensed in California in 1920. Dr. Broemser was a member of the Santa Clara County Medical Society.

BURCH, ARTHUR BENJAMIN, Berkeley. Died January 12, 1976 in Berkeley, aged 68. Graduate of the University of California Medical School, Berkeley-San Francisco, 1946. Licensed in California in 1947. Dr. Burch was a member of the Alameda-Contra Costa Medical Association.

CLEARY, ERNEST WINTON, San Mateo. Died January 29, 1976 in San Mateo, aged 95. Graduate of the University of California Medical School, Berkeley-San Francisco, 1912. Licensed in California in 1912. Dr. Cleary was a retired member of the San Mateo County Medical Society.

EDMAN, CHARLES RAYMOND, San Jose. Died February 14, 1976 in Los Gatos, aged 50. Graduate of the University of Illinois College of Medicine, Chicago, 1953. Licensed in California in 1954. Dr. Edman was a member of the Santa Clara County Medical Society.

GURZA, AGUSTIN, San Jose. Died February 18, 1976 in San Jose of heart disease, aged 57. Graduate of Universidad Nacional Facultad de Medicina, México, D.F., 1941. Licensed in California in 1954. Dr. Gurza was a member of the Santa Clara County Medical Society.

HEADLEY, NATHAN E., Palm Desert. Died January 21, 1976 in Palm Desert of periarteritis nodosa, aged 63. Graduate of the Ohio State University College of Medicine, Columbus, 1941. Licensed in California in 1948. Dr. Headley was a member of the Los Angeles County Medical Association.

HESSING, ERNEST EMANUEL, Oakland. Died February 18, 1976 in Berkeley of heart disease, aged 74. Graduate of Johann Wolfgang Goethe-Universität Medizinische Fakultät, Frankfurt-am-Main, 1924. Licensed in California in 1935. Dr. Hessing was a member of the Alameda-Contra Costa Medical Association.

MARTINS, SAMUEL MARION, La Canada. Died January 31, 1976 of heart disease, aged 72. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1929. Licensed in California in 1929. Dr. Martins was a member of the Los Angeles County Medical Association.

MEININGER, WILLARD MERLE, Sacramento. Died January 21, 1976 in Sacramento, aged 68. Graduate of the University of Nebraska College of Medicine, Omaha, 1930. Licensed in California in 1931. Dr. Meininger was a retired member of the Sacramento County Medical Association.

PADDEN, EDMUND H., Oakland. Died February 9, 1976 in Palo Alto of pneumonia, aged 78. Graduate of the University of Oregon Medical School, Portland, 1922. Licensed in California in 1929. Dr. Padden was a member of the Alameda-Contra Costa Medical Association.

SCHNOOR, ERNEST E., Redwood City. Died February 7, 1976 in a glider crash on the Mission Peak Range near Fremont, aged 55. Graduate of Duke University School of Medicine, Durham, 1951. Licensed in California in 1952. Dr. Schnoor was a member of the San Mateo County Medical Society.

STEINSAPIR, LEON JULIUS, Sacramento. Died January 31, 1976 in Sacramento of heart disease, aged 47. Graduate of State University of New York College of Medicine at New York City, 1953. Licensed in California in 1958. Dr. Steinsapir was a member of the Sacramento County Medical Association.

VAN METER, J. RAY, Palo Alto. Died January 11, 1976 at Stanford University Medical Center of heart disease, aged 75. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1928. Licensed in California in 1946. Dr. Van Meter was a retired member of the Santa Clara County Medical Society.

WARD, ROBERTSON, Kentfield. Died February 5, 1976 in Kentfield, aged 79. Graduate of the University of California Medical School, Berkeley-San Francisco, 1924. Licensed in California in 1924. Dr. Ward was a retired member of the Marin Medical Society.

WILLOUGHBY, ROSS WARRINGTON, Fresno. Died January 21, 1976 in Clovis, aged 54. Graduate of the University of Toronto Faculty of Medicine, 1946. Licensed in California in 1949. Dr. Willoughby was a member of the Fresno-Madera Medical Society.

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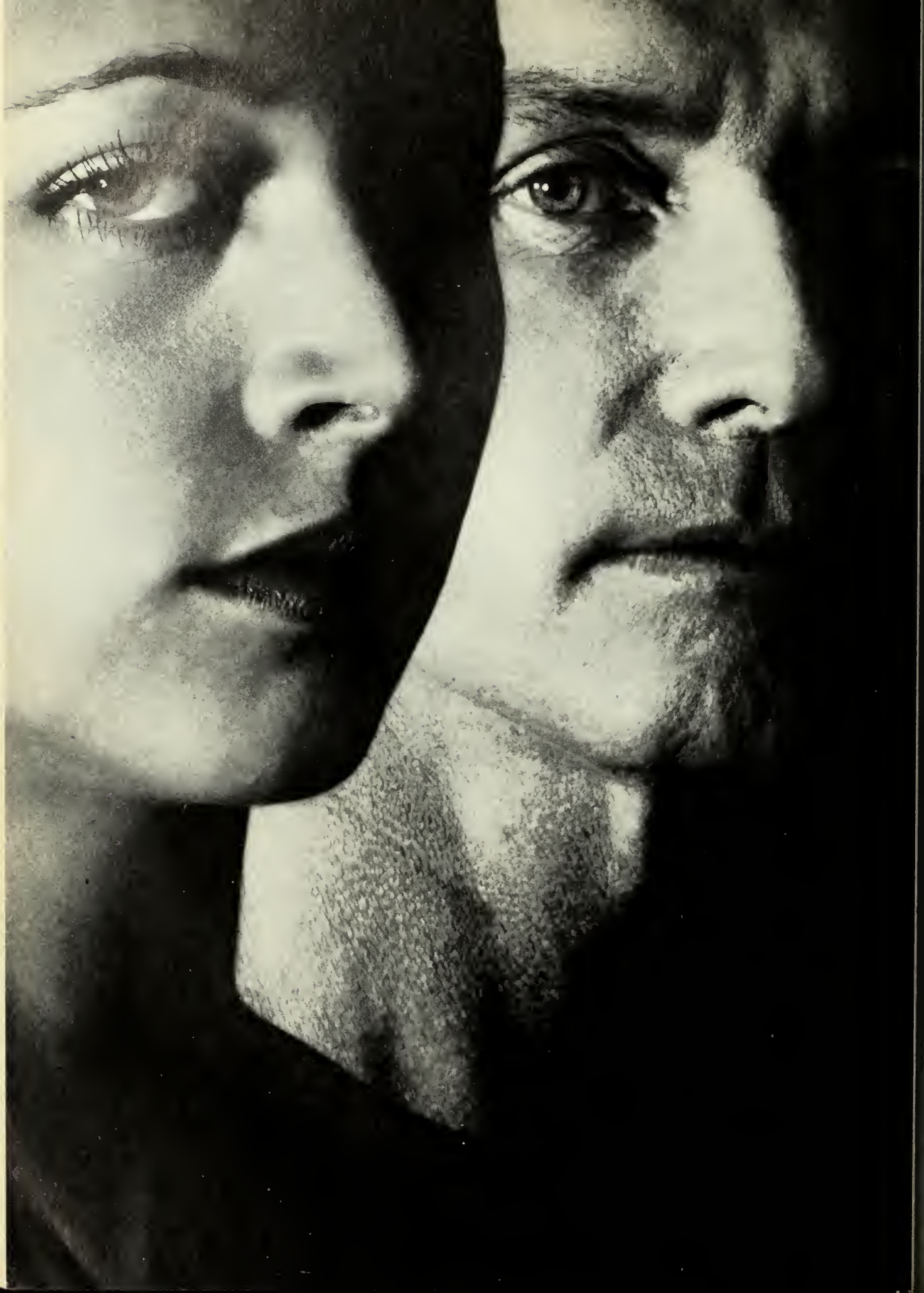

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the weight of ethical opinion:

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The Pharmaceutical Manufacturers Association represents firms that are significantly engaged in the discovery and development of new medicines, medical devices and diagnostic products. Clinical research is essential to their efforts. Consequently, PMA formulated positions which it submitted on July 11, 1975, to the Subcommittee on Health of the Senate Labor and Public Welfare Committee, as its official policy recommendations. Here are the essentials of PMA's current thinking in this vital area.

1. PMA supports the mandate and mission of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and offers to establish a special committee composed of experts of appropriate disciplines familiar with the industry's research methodology to volunteer its service to the Commission.

2. PMA supports the formation of an independent, expert, broadly based and representative panel to assess the current state of drug innovation and the impact upon it of existing laws, regulations and procedures.

3. When FDA proposes regulations, it should prepare and publish in the *Federal Register* a detailed statement assessing the impact of those regulations on drug and device innovation.

4. PMA proposes that an appropriately qualified medical organization be encouraged to undertake a comprehensive study of the optimum roles and responsibilities of the sponsor and physician when company-sponsored clinical research is performed by independent clinical investigators.

5. PMA recognizes that the physician-investigator has, and should have, the ultimate responsibility for deciding the substance and form of the informed consent to be obtained. However, PMA recommends that the sponsor of the experiment aid the investigator in discharging this important responsibility by providing (1) a document detailing the investigator's responsibilities under FDA regulations with regard to patient consent, and (2) a written description of the relevant facts about the investigational item to be studied, in comprehensible lay language.

6. In the case of children, the sponsor must require that informed consent be obtained from a legally appropriate representative of the participant. Voluntary consent of an older child, who may be capable of understanding, in addition to that of a parent, guardian or other legally responsible person, is advisable. Safety of the drug or device shall have been assessed in adult populations prior to use in children.

7. PMA endorses the general principle that, in the case of the mentally infirm, consent should be sought from both an understanding subject and from a parent or guardian, or in their absence, another legally responsible person.

8. Pharmaceutical manufacturers sponsoring investigations in prisons must take all reasonable care to assure that the facilities and personnel used in the conduct of the investigations are suitable for the protection of participants, and for the avoidance of coercion, with a respect for basic humanitarian principles.

9. Sponsors intending to conduct non-therapeutic clinical trials through the participation of employee volunteers should expand the membership and scope of its existing Medical Research Committee, or establish such an internal Medical Research Committee, with responsibility to approve the consent forms of all volunteers, designs, protocols and the scope of the trial. The Committee should also bear responsibility to ensure full compliance with all procedures intended to protect employee volunteers' rights.

10. Where the sponsor obtains medical information or data on individuals, it shall be accorded the same confidential status as provided in codes of ethics governing health care professionals.

11. PMA and its member firms accept responsibility to aid and encourage appropriate follow-up of human subjects who have received investigational products that cause latent toxicity in animals or, during their use in clinical investigation, are found to cause unexpected and serious adverse effects.

12. PMA supports the exploration and development by its member companies of more systematic surveillance procedures for newly marketed products.

13. When a pharmaceutical manufacturer concludes, on the basis of early clinical trials of a basic new agent, that a new drug application is likely to be submitted, a proposed development plan accompanied by a summary of existing data, would be submitted to the FDA. Following a review of this submission, the FDA, and its Advisory Committee where appropriate, would meet with the sponsor to discuss the development plan. No *formal* FDA approval should be required at this stage. Rather, the emphasis should be on identification of potential problems and questions for the sponsor's further study and resolution as the program develops.

The PMA believes that health professionals as well as the public at large should be made aware of these 13 points in its Policy on Clinical Research. For these recommendations envisage constructive, cooperative action by industry, research institutions, the health professions and government to encourage creative and workable responses to issues involved in the clinical investigation of new products.

P·M·A

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(Continued from Page 18)

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COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: For a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education, please write to the above address.

ALCOHOLISM AND DRUG ABUSE

May 21-23—**Alcoholism and Drug Abuse.** UCSF. Friday-Sunday.

May 27-29—**National Conference on Radiation Oncology.** American Cancer Society at Hilton Hotel, San Francisco. Thursday-Saturday. Contact: S. L. Arje, MD, ACS, 777 3rd Ave., New York 10017.

CANCER

May 1—**Cancer Viewpoint Symposium—6th Annual.** Contra Costa Unit, American Cancer Society, at John Muir Hospital, Walnut Creek. Saturday. 5 hrs. $14. Contact: Bernard Larner, MD, 1601 Ygnacio Valley Rd., Walnut Creek 94598. (415) 939-3000.

June 21-25—**Head and Neck Oncology.** UCLA. Monday-Friday.

MEDICINE

April 26-30—**Advances in Internal Medicine.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday.

April 29—**Annual Physicians' Cardiovascular Symposium—Cardiology 1976.** American Heart Association, Central Valley Chapter, at Hilton Hotel, Fresno. Thursday. $35. Contact: AHA, Central Valley Chapter, 3835 N. West Ave., Fresno 93705. (209) 224-8215.

April 30—**Flexible Bronchofibroscopy II.** PMC. Friday.

May 6-8—**Arrhythmias: Basic and Clinical Aspects.** PMC at Golden Gateway Holiday Inn, San Francisco. Thursday-Saturday.

May 7-8—**Coagulation Update 1976.** UCSF. Friday-Saturday.

May 14—**American Heart Association, California Affiliate—Scientific Sessions for Physicians.** Hotel Del Coronado, Coronado. Friday. 6½ hrs. $25. Contact: Marilyn Probst, Admin. Asst., AHA, Calif. Affiliate, 1370 Mission St., San Francisco. (415) 626-0123.

May 18—**Seminars in Nephrology.** USC. Tuesday.

May 21—**Diagnosis and Treatment of Hypertension.** PMC. Friday.

May 22-23—**Dermatology/Hematology.** UCLA. Saturday-Sunday.

June 8-11—**Core Curriculum in Echocardiography: New Developments in Cardiac Ultrasound.** American College of Cardiology, San Diego County Heart Assn., UCSD, Naval Regional Medical Center, at Town and Country Hotel, San Diego. Tuesday-Friday. Contact: ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

June 18—**Allergy for the Busy Office Practice.** PMC. Friday.

June 23-25—**The Endocrine Society—58th Annual Meeting.** Hilton Hotel, San Francisco. Wednesday-Friday. Contact: The Endocrine Society Annual Meeting Office, 9650 Rockville Pike, Bethesda, Md. 20014.

June 26—**EKG Workshop.** PMC at Golden Gateway Holiday Inn, San Francisco. Saturday. $70.

June 29-July 2—**Interpretative Enzymology.** UCSD. Tuesday-Friday.

July 12-15—**2nd International Symposium on Psoriasis.** STAN. Monday-Thursday.

August 3—**Seminars in Nephrology.** USC. Tuesday.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

August 25-27—**Cardiology Today: For the Physician in Clinical Practice.** Mt. Zion Hospital and Medical Center, Univ. of Pittsburgh School of Medicine, under auspices of the Council on Clinical Cardiology of American Heart Assn., at St. Francis Hotel, San Francisco. Wednesday-Friday. Contact: Cont. Education, Mt. Zion Hospital & Medical Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2401.

August 29-September 4—**In-Depth Nephrology Board Review Course.** Cedars-Sinai Medical Center at Beverly Hilton Hotel, Los Angeles. One week. 60 hrs. $300. Contact: Andrew Lewin, MD, Renal Hypertension, Cedars-Sinai Medical Center, P.O. Box 48750, Los Angeles 90048. (213) 855-4671.

OBSTETRICS AND GYNECOLOGY

May 15-16—**Gyn-Urology.** USC at Biltmore Hotel, Santa Barbara. Saturday-Sunday.

PEDIATRICS

April 23-24—**Pediatric Ophthalmology.** See Surgery, April 23-24.

April 24-May 1—**Pediatric Review.** USC at Maui Surf, Hawaii. One week.

April 29-May 1—**Current Concepts in Children's Orthopaedics.** See Surgery, April 29-May 1.

May 3-7—**Pediatric Review—6th Annual.** USC. Monday-Friday.

May 8-9—**Learning Disabilities in Children.** UCLA. Saturday-Sunday.

May 13-15—**Annual Pediatric Course.** UCSF. Thursday-Saturday.

May 21-23—**American Academy of Pediatrics, California Chapter I, District IX.** Ahwahnee Hotel, Yosemite. Friday-Sunday. Contact: Melvin H. Schwartz, MD, 2219 Santa Clara Ave., Alameda 94501.

May 23-26—**Recent Advances in Pediatric Neurology.** UCLA at Ahwahnee Hotel, Yosemite. Sunday-Wednesday.

June 11—**Conference on Prematurity—15th Annual.** STAN. Friday.

June 11-12—**Depression in Children.** See Psychiatry, June 11-12.

PSYCHIATRY

May 8-9—**Learning Disabilities in Children.** See Pediatrics, May 8-9.

May 16-19—**Biofeedback—3rd Annual Program.** UCLA at Ahwahnee Hotel, Yosemite. Sunday-Wednesday.

June 11-12—**Depression in Children.** UCD at Marriott Inn, Berkeley. Friday-Saturday.

June 11-12—**Human Behavior.** USC. Friday-Saturday.

June 18-19—**Clinical Biofeedback in Medicine: Psychiatry and Psychology.** UCD at Claremont Hotel, Oakland. Friday-Saturday.

June 19-20—**Advanced Psychotherapeutic Techniques.** UCLA. Saturday-Sunday.

RADIOLOGY AND PATHOLOGY

May 5-8—**Nuclear Medicine—6th Annual Spring Symposium.** Sierra Valley Nuclear Medicine Assn.; No. Calif. Chapter, Society of Nuclear Medicine, at Convention Center, Lake Tahoe. Wednesday-Saturday. Contact: Darleen Nelson, Nuclear Medicine Dept., Mercy San Juan Hospital, 6501 Coyle Ave., Carmichael 95608.

June 11-13—**American Association of Neuropathologists—Annual Meeting.** Hyatt Regency, San Francisco. Friday-Sunday. Contact: Richard L. Davis, MD, LAC-USC Medical Center, 1200 N. State St., Los Angeles 90033. (213) 226-7123.

SURGERY AND ANESTHESIOLOGY

April 22-23—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

April 22-24—**General Surgery—Annual Course.** UCSF at Hilton Hotel, San Francisco. Thursday-Saturday.

April 23-24—**Pediatric Ophthalmology—A Current Review—7th Annual Jules Stein Lecture and Postgraduate Seminar.** Jules Stein Eye Institute at Beverly Hilton Hotel, Los Angeles. Friday-Saturday. Contact: Jules Stein Eye Institute, UCLA.

April 23-25—**American Association for Thoracic Surgery.** Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Mr. W. T. Maloney, Exec. Sec., 6 Beacon St., Suite 620, Boston, Mass. 02108. (617) 227-0760.

April 29-May 1—**Current Concepts in Children's Orthopaedics.** American Academy of Orthopaedic Surgeons, Committee on Pediatric Orthopaedics, at Vacation Village Hotel, San Diego. Thursday-Saturday. $150 for AAOS members; $200, nonmembers. Contact: AAOS, 430 N. Michigan Ave., Chicago 60611.

May 1-8—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

May 4-7—**Samuel Higby Camp—Orthopedic Surgery.** UCSF. Tuesday-Friday.

May 15-16—**Gynecology-Urology.** See Obstetrics and Gynecology, May 15-16.

May 16-28—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. 100 hrs. $1,200 for otolaryngologists; $900 for residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

May 20-21—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

May 20-22—**Neurosurgery—6th Annual Postgraduate Course.** UCSF at St. Francis Hotel, San Francisco. Thursday-Saturday.

May 23-26—**Recent Advances in Pediatric Neurology.** See Pediatrics, May 23-26.

June 3-5—**Highlights of Ophthalmology.** PMC at Golden Gateway Holiday Inn, San Francisco. Thursday-Saturday.

June 4—**Phacoemulsification Surgery Course.** Jules Stein Eye Institute, Los Angeles. Friday. $250. Contact: Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles.

June 5—**Sports Medicine.** See Of Interest To All, June 5.

June 10-11—**Trauma.** UCSF at Mary's Help Hospital, Daly City. Thursday-Friday.

June 10-12—**Glaucoma.** UCSF at Quail Lodge, Monterey. Thursday-Saturday.

June 12-13—**Modern Laryngoscopy and Bronchoesophagoscopy: A Theoretical and Practical Course.** UCLA. Saturday-Sunday. $300; $150, residents. Contact: Paul H. Ward, MD, Division of Head and Neck Surgery, UCLA School of Medicine, Los Angeles 90024.

June 13-20—**Orthopedic Review.** USC at Mauna Kea, Hawaii. One week.

June 24-25—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

June 26—**Clinical Conference in Ophthalmology.** STAN. Saturday. 7 hrs. $35.

August 1-13—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. 100 hrs. $1,200 for otolaryngologists; $900, residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

(Continued on Page 32)

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Diagnosis and Prognosis of Depression and Anxiety

MATTHEW BLOCK, PhD, MD — **JULY 31-AUGUST 1**
Professor of Medicine, University of Colorado
Blood Diseases: Current Practice

JOSEPH FINNEY, PhD, MD — **AUGUST 7-8**
Professor of Education, University of Kentucky
Modern Diagnosis of Emotional Conditions

GEORGE DE VOS, PhD — **AUGUST 14-15**
Professor of Anthropology, University of California
Diagnosis Across Racial-Cultural Bounds

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(Continued from Page 30)

August 15-18—**Urology.** UCLA at Lake Arrowhead. Sunday-Wednesday.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

April 23-24—**West Coast Counties Postgraduate Institute.** CMA at Quail Lodge, Carmel Valley. 14 hrs. $60 for CMA members; $90, non-members. Friday-Saturday. Contact: Richard Manley, CMA.

April 24—**5th Annual Symposium—Fluid and Electrolytes—Management in Clinical Practice.** South Coast Community Hospital, South Laguna. Saturday. 8 hrs. $25. Contact: Eugene B. Levin, MD, Dir. of Med. Ed., SCCH, 31872 Coast Highway, South Laguna 92677. (714) 499-1311, ext. 136-137.

April 26-May 1—**Emergency Medicine.** USC at Kauai Surf, Kauai, Hawaii. Monday-Saturday.

April 26-May 1—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Saturday.

April 29-May 1—**Psychosocial Care of Dying Patient—Doctor:Patient Relationship.** UCSF at St. Francis Hotel, San Francisco. Thursday-Saturday.

April 29-May 2—**Medicine and Related Techniques in the Treatment of Musculoskeletal Pain.** USC. Thursday-Sunday.

May 5-8—**American College of Sports Medicine—23rd Annual Meeting.** Disneyland Hotel, Anaheim. Wednesday-Saturday. Contact: ACSM, 1440 Monroe St., Madison, Wisconsin 53706.

May 10-15—**Diving Medicine.** UCSF at VA Hospital, Fresno. Monday-Saturday.

May 10-21—**Family Practice—Intensive Review.** USC. Two weeks.

May 14-15—**San Joaquin Valley Counties Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Friday-Saturday. $60 for CMA members; $90, non-members. Contact: Richard Manley, CMA.

May 15—**Clinical Pharmacology Conference.** Stanford Division of Clinical Pharmacology and Palo Alto Medical Research Foundation at Stanford. Saturday. Contact: STAN.

May 17-21—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

May 19-22—**American College of Emergency Physicians, California Chapter—5th Annual Scientific Assembly.** Sheraton-Universal Hotel, North Hollywood. Wednesday-Saturday. $100 for members; $125, nonmembers. Contact: Stephanie McWilliams, Assembly Coordinator, 58 California Ave., Orinda 94563. (415) 254-1332.

May 21—**Diagnosis and Treatment of Hypertension.** See Medicine, May 21.

May 29-30—**Opportunistic Fungus Diseases.** UCSF. Saturday-Sunday.

June 3-4—**Mosquito Attractants and Repellents.** UCSF. Friday-Saturday.

June 5—**Sports Medicine.** UCD at Sacramento Inn, Sacramento. Saturday.

June 10-12—**Management of Medical Problems for Family Physicians.** PMC at Golden Gateway Holiday Inn, San Francisco. Thursday-Saturday.

July 5-9—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD. Monday-Friday.

August 2-6—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday.

August 18-22—**Family Practice Refresher Course—3rd Annual.** UCLA. Wednesday-Sunday.

August 22-27—**Family Practice Refresher Course.** UCD at Del Monte Hyatt, Monterey. Sunday-Friday.

Audio-Digest Foundation. A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: Family Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $90 per year. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90057. (213) 483-3451.

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Providence Medical Center, 700 NE 47th Avenue, Portland 97213. Contact: Dave Gilbert, MD, Providence Medical Center:

Every Wednesday, 8:00 a.m. to 9:00 a.m.—**Spring Medical Grand Rounds.**

University of Oregon Medical School, Family Practice Center, 3181 S.W. Sam Jackson Park Road, Portland 97201:

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School.

FAMILY PRACTICE

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Family Practice Center, University of Oregon Medical School, Portland. Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

May 20—**Woodland Park Hospital Family Practice Symposium.** Woodland Park Hospital, Portland. Contact: R. T. Gustafson, MD, 10300 N.E. Hancock Street, Portland, 97220.

INTERNAL MEDICINE

May 20-22—**Oregon Society of Internal Medicine Annual Meeting.** Sunriver Lodge, Sunriver, Oregon. Contact: Donald R. Olson, MD, Oregon Society of Internal Medicine, 2164 S.W. Park Place, Portland 97205.

PHYSICAL MEDICINE AND REHABILITATION

April 30-May 1—**Northwest Association of Physical Medicine and Rehabilitation Annual Meeting.** Jantzen Beach Thunderbird, Portland. Contact: John E. Stanwood, MD, Emanuel Hospital, 2801 N. Gantenbein, Emanuel East, Room 370, Portland 97227.

SURGERY

April 2-3—**American College of Foot Surgeons, Western Division.** Portland Hilton Hotel, Portland. Contact: Robert L. Rutherford, D.P.M., 400 - 40th Street, Oakland, California 94609

September 6-7—**Western Orthopedic Society Annual Meeting.** Sunriver Lodge, Bend. Contact: Stanley E. Donahoo, MD, 1819 West Harvard Blvd., Roseburg 97470.

OF INTEREST TO ALL PHYSICIANS

April 14-15—**Treating Occupational Injuries.** Sheraton Motor Hotel, Portland. Contact: Rollan A. Martin, MD, Workmen's Compensation Board of the State of Oregon, 201 Labor and Industries Building, Salem, 97310.

September 22-24—**Oregon Medical Association Annual Scientific Session.** Hilton Hotel, Portland. Contact: Sondra Gleason, Oregon Medical Association, 2164 S.W. Park Place, Portland 97205.

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In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

April 12-16—**Emergency Medicine Institute.** Monday-Friday. Univ. of Wash. Sch. of Med., Seattle. Limited to 16. 38 hrs. $275. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 22-23—**Respiratory Care Conference.** Thursday-Friday. Olympic Hotel, Seattle. Hours and fees to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 24—**Current Concepts in Nutrition.** Saturday. University Tower Hotel, Seattle. 6 hrs. WSDA. $21. Contact Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

April 30—**Medicine and Law.** Friday. Seattle. Location, hours and fees to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 1—**Current Concepts in Nutrition.** Saturday. Deaconess Hospital School of Nursing, Spokane. 6 hrs., WSDA. $21. Contact Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 6-7—**Surgical Therapeutics.** Thursday-Friday. Washington Plaza Hotel, Seattle. Limited to 200. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 7-8—**Regional Block Anesthesia.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

May 9-10—**Postgraduate Conference for Physicians.** Sunday-Monday. Billings, Montana. Contact: John P. Connor, Exec. Dir., Montana State Heart Assoc., 510 First Ave. N., Great Falls 59401. (406) 452-2362.

May 12-14—**Advances in Internal Medicine.** Wednesday-Friday. Olympic Hotel, Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 16-20—**Pacific Coast Oto-Ophthalmological Society.** Sunday-Wednesday. Washington Plaza Hotel, Seattle. Contact: M. F. W. Smith, MD, Ear Medical Clinic of Santa Clara Valley, 2120 Forest Ave., Suite 2, San Jose, CA 95128.

May 20-21—**Pediatric Care for General Practitioners.** Thursday-Friday. Children's Orthopaedic Hospital and Medical Center, Seattle. 12 hrs. $45. Contact: William O. Robertson, MD, Dir. Med. Ed., Children's Orthopaedic Hospital and Medical Center, 4800 Sand Point Way NE, Seattle 98105. (206) 634-5072.

May 21-22—**Sports Medicine—1976.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

May 24-28—**Treating the Untreatable—Univ. of Washington School of Medicine's Montana Circuit Course.** Great Falls, 24th; Billings, 25th; Bozeman, 26th; Missoula, 27th; Whitefish/Kalispell, 28th. 4 hrs. Physicians, $25; others, $10. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

June 2-4—**Alaska State Medical Association Annual Meeting.** Wednesday-Friday. Anchorage. Contact: Alaska State Medical Association, 1135 W. 8th Ave., Anchorage, AK 99501.

June 10-11—**Hypertension: Etiology and Factors in Choice of Drugs.** Thursday-Friday. Virginia Mason Medical Center Auditorium, Seattle. 12 hrs. $75. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

June 14-17—**Disorders of Red Cell Proliferation.** (ACP). Sunday-Thursday. Rosario Resort, Orcas Island, WA. Hours to be determined. ASH, ACP members, fellows, residents, $140; non-members, $195; associates, $70. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

June 17-19—**Behavioral Methods in Medical Practice.** Thursday-Saturday. University Tower Hotel, Seattle. 8 hrs, $60. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

June 25—**Bicentennial History of Medicine in the United States.** Friday. Kane Hall, Univ. of Wash., Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

July 26-29—**World of the Heart and Lung: America's Hearts and Lungs After 200 Years.** Monday-Thursday. University Tower Hotel, Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

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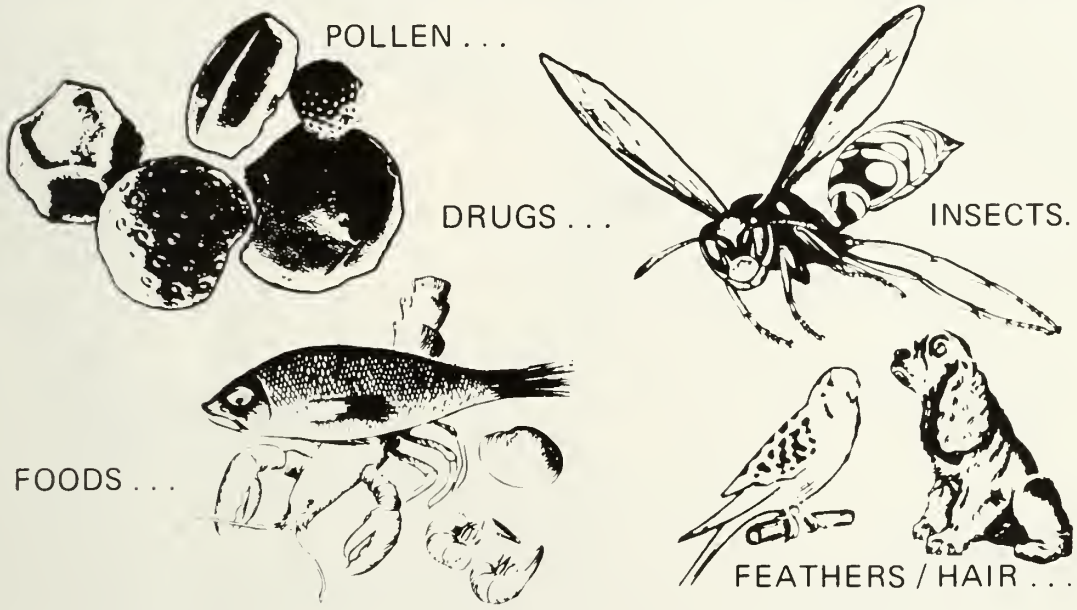

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REFERENCES

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Vol. 49, No. 1-9, 1972

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An In Vitro Test as used in the detection of immediate hypersensitivity in man.
V Latin American Congress of Allergy and Immunology National Academy of Medicine
Buenos Aires, Argentina, October 1974

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- ☐ effective, reliable oral analgesia in moderate to moderately severe pain
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- ☐ one tablet q.6 h.*

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Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (Warning: May be habit forming), 0.38 mg. oxycodone terephthalate (Warning: May be habit forming), 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine

Ⓒ II

*See dosage and administration section of Brief Summary

Whenever an APC/narcotic is indicated.

DESCRIPTION Each yellow scored tablet contains 4.50 mg oxycodone HCl (Warning May be habit forming), 0.38 mg oxycodone terephthalate (Warning May be habit forming), 224 mg aspirin, 160 mg phenacetin, and 32 mg caffeine

INDICATIONS For the relief of moderate to moderately severe pain

CONTRAINDICATIONS Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCODAN®, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications Like other narcotic-containing medications, PERCODAN® is subject to the Federal Controlled Substances Act

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery The patient using PERCODAN® should be cautioned accordingly

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCODAN® may exhibit an additive CNS depression When such combined therapy is contemplated, the dose of one or both agents should be reduced

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development Therefore, PERCODAN® should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCODAN® should not be administered to children PERCODAN®-Demi, containing half the amount of oxycodone can be considered. (See product prescribing information for PERCODAN®-Demi.)

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCODAN® or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCODAN® should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may be occasionally necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCODAN® is given orally The usual adult dose is one tablet every 6 hours as needed for pain

DRUG INTERACTIONS The CNS depressant effects of PERCODAN® may be additive with that of other CNS depressants. See WARNINGS.

Aspirin may enhance the effect of anticoagulants and inhibit the uricosuric effect of uricosuric agents.

MANAGEMENT OF OVERDOSAGE Signs and Symptoms Serious overdose with PERCODAN® is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur. The ingestion of very large amounts of PERCODAN® may, in addition, result in acute salicylate intoxication.

Treatment Primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonists naloxone, nalorphine or levallorphan are specific antidotes against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including oxycodone Therefore, an appropriate dose of one of these antagonists should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated

Gastric emptying may be useful in removing unabsorbed drug

DEA Order Form Required.

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Effectiveness across the spectrum of most common forms of insomnia

Awake too long, awake too often, awake too early...

These are the most common forms of insomnia, and may occur singly or in any combination. The night of troubled sleep depicted here comprises all three types. As the night progresses from left to right, each sleep stage is identifiable by its own shade of gray. Blue represents "Awake."

As you can see, this hypothetical "patient" takes well over an hour to fall asleep, awakens several times during the middle of the night and awakens too early in the morning.

Sleep Stages

- Awake
- REM
- Stage 1
- Stage 2
- Stage 3
- Stage 4

Awake too long

Awake too often during the night

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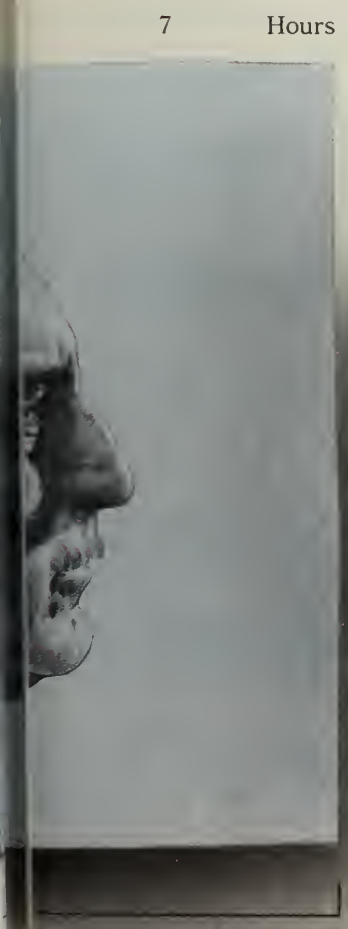
The insomnias most often occurring in young and older adults

For patients with trouble falling asleep (common in young adult insomnia patients), Dalmane (flurazepam HCl) 30 mg provides sleep within 17 minutes, on average. For those with trouble staying asleep or sleeping long enough (common in those over 50), Dalmane offers increased total sleep time with fewer nocturnal awakenings. These clinical results were demonstrated in studies conducted in four geographically separated sleep research laboratories.[1-4]

The relative safety of Dalmane (flurazepam HCl) is well documented

Dalmane (flurazepam HCl) is relatively safe and well tolerated; morning "hang-over" has been infrequent. The usual adult dosage is 30 mg; in elderly or debilitated patients, limit initial dosage to 15 mg to preclude over-sedation, dizziness or ataxia. Caution patients about possible combined effects with alcohol and other CNS depressants.

Broad-spectrum medication for the most common forms of insomnia



Awake too early

Dalmane®
(flurazepam HCl)

One 30-mg capsule *h.s.*— usual adult dosage
(15 mg may suffice in some patients).
One 15-mg capsule *h.s.*— initial dosage for elderly or debilitated patients.

- induces sleep rapidly
- reduces nighttime awakenings
- lengthens total sleep time

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Please see following page for a summary of complete product information.

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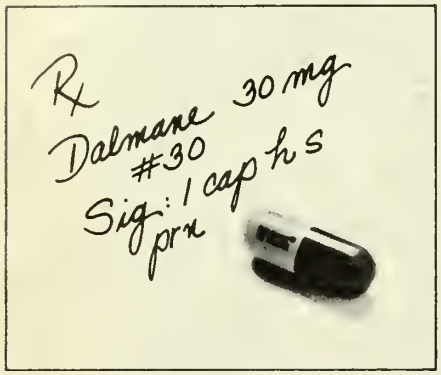

Objectively proved in the sleep research laboratory, Dalmane

- □ induces sleep within 17 minutes, on average
- □ reduces nighttime awakenings
- □ provides 7 to 8 hours sleep, on average, without repeating dosage

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Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

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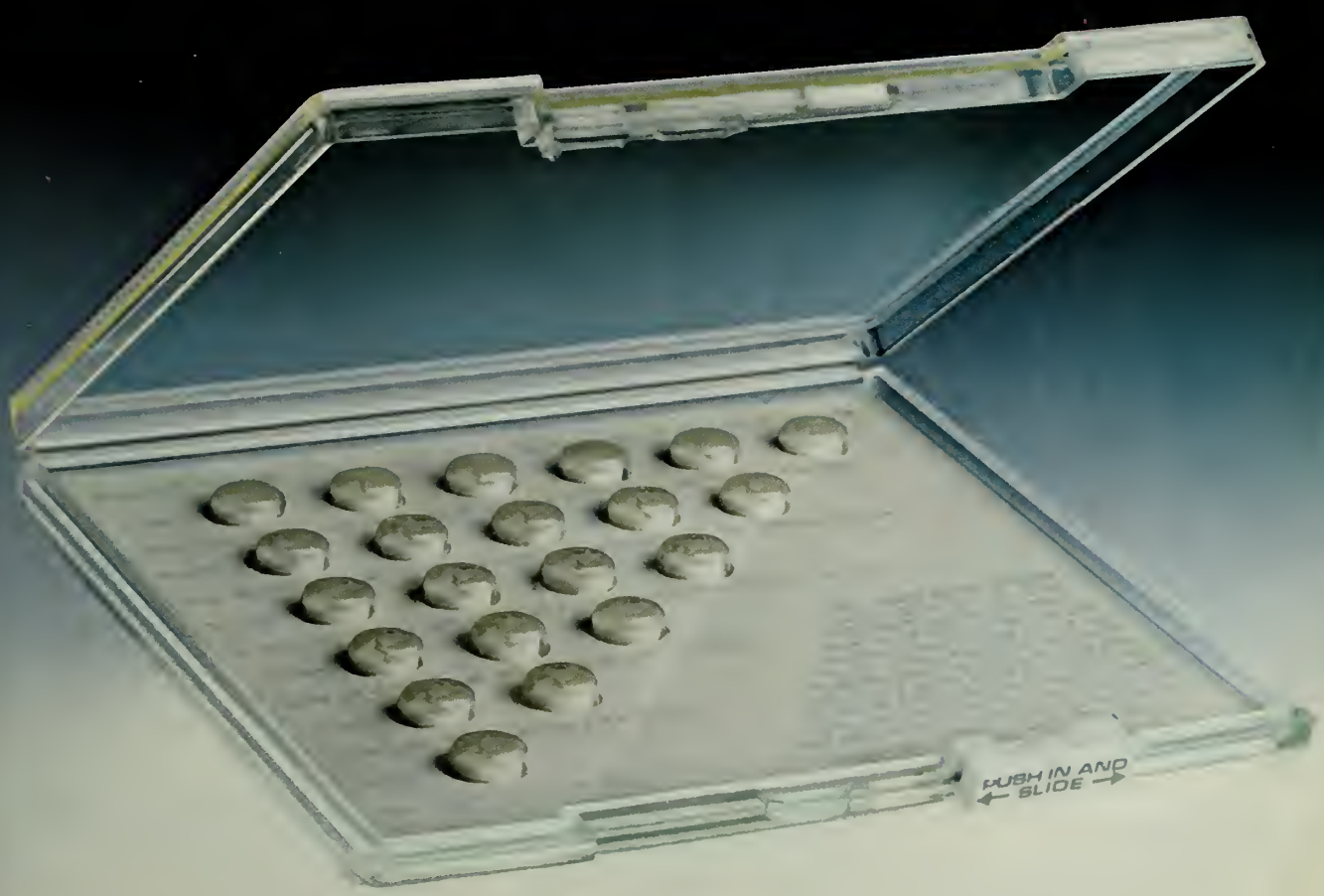

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- ☐ one tablet q.6 h.*

Percodan® Tablets

Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (Warning: May be habit forming), 0.38 mg. oxycodone terephthalate (Warning: May be habit forming), 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine. (II)

*See dosage and administration section of Brief Summary

Whenever an APC/narcotic is indicated.

DESCRIPTION Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (Warning: May be habit forming), 0.38 mg. oxycodone terephthalate (Warning: May be habit forming), 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine.

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCODAN®, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCODAN® is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCODAN® should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCODAN® may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCODAN® should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCODAN® should not be administered to children. PERCODAN®-Demi, containing half the amount of oxycodone, can be considered. (See product prescribing information for PERCODAN®-Demi.)

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCODAN® or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCODAN® should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may be occasionally necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCODAN® is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCODAN® may be additive with that of other CNS depressants. See WARNINGS.

Aspirin may enhance the effect of anticoagulants and inhibit the uricosuric effect of uricosuric agents.

MANAGEMENT OF OVERDOSAGE Signs and Symptoms Serious overdose with PERCODAN® is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur. The ingestion of very large amounts of PERCODAN® may, in addition, result in acute salicylate intoxication.

Treatment Primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonists naloxone, nalorphine or levallorphan are specific antidotes against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including oxycodone. Therefore, an appropriate dose of one of these antagonists should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

DEA Order Form Required.

PERCODAN® is a registered trademark of Endo, Inc.

Endo Inc.
Manati, Puerto Rico 00701
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)

EDO 6750

Schering

In serious gram-negative infections*

Three good reasons to initiate therapy with Garamycin® Injectable

(gentamicin sulfate)

1. Unique spectrum.

2. Incidence of bacterial resistance is low and has not increased significantly.

3. Relatively low order of adverse renal and eighth nerve reactions when used as directed.

*Due to susceptible organisms

1. Unique spectrum.

Garamycin Injectable (gentamicin sulfate) is active against susceptible strains of seven major gram-negative pathogens. These are:

Escherichia coli
Proteus, indole-negative
Proteus, indole-positive
Pseudomonas aeruginosa
Klebsiella
Enterobacter } species
Serratia

Garamycin Injectable is also highly effective against susceptible strains of **Staphylococcus aureus** and may be considered when penicillins are contraindicated.

Escherichia coli | *Proteus* species, indole-negative | *Proteus* species, indole-positive | *Pseudomonas aeruginosa* | *Klebsiella* | *Enterobacter* | *Serrati*

2. Incidence of bacterial resistance is low and has not increased significantly

*In vitro** susceptibility virtually unchanged

* *In vitro* susceptibility data are not necessarily indicative of clinical effectiveness.

In a five-year study[1] in over 180 hospitals, gram-negative pathogens identified and tested demonstrated high susceptibility to GARAMYCIN. From 1971 through 1975 there was virtually no change in the percentage of strains of major gram-negative pathogens susceptible to GARAMYCIN.

In the seven or eight years' experience of one investigator[2] where gentamicin has been restricted to parenteral use, resistance has not appreciably changed.

Resistance has been demonstrated to develop slowly in stepwise fashion. No one-step mutations to high resistance have been reported.

References

1. P.M.R. Bacteriologic Reports—1971-1975.
2. Jackson, G.G.: Highlights of a Symposium on Gentamicin, a filmed panel discussion summarizing a symposium on gentamicin, University of California School of Medicine, Los Angeles, January 26, 1971.

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3. Relatively low order of adverse renal and eighth nerve reactions when used as directed.

Schering

Adverse renal reactions

The risk of adverse renal reactions is low in patients with normal renal function. Usually manifested by nitrogen retention as evidenced by a rising BUN and creatinine, they occur most often in patients with pre-existing renal damage and in patients receiving larger than recommended doses treated for longer periods of time than recommended. See Warning Box below.

Adverse eighth nerve reactions

The incidence of adverse eighth nerve reactions with GARAMYCIN Injectable is relatively low. When occurring, the effect is predominantly on the vestibular branch of the eighth cranial nerve, resulting in vestibular dysfunction with vertigo and tinnitus. These symptoms have, in many cases, been transitory. The known effect on the auditory branch to date mostly has involved only the high-frequency hearing ranges. See Warning Box below.

A logical choice

in serious gram-negative infections†

- pneumonia
- urinary tract infections
- septicemia
- wound infections

† Due to susceptible organisms

Garamycin® I.M./I.V.

gentamicin sulfate injectable **80mg/2ml.**

40 mg /ml Each ml contains gentamicin sulfate equivalent to 40 mg of gentamicin

WARNING

Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug

Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable, usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment

Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug

In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg /ml. should be avoided

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity

USAGE IN PREGNANCY Safety for use in pregnancy has not been established

See Clinical Considerations section which follows.

A logical choice
in serious gram-negative infections

Schering

GARAMYCIN® Injectable, brand of gentamicin sulfate, U.S.P., injection, 40 mg. per ml.
Each ml. contains gentamicin sulfate, U.S.P. equivalent to 40 mg. gentamicin.
For Parenteral Administration.

WARNING

Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

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The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY Safety for use in pregnancy has not been established.

INDICATIONS GARAMYCIN Injectable is indicated, with due regard for relative toxicity of antibiotics, in the treatment of serious infections caused by susceptible strains of the following microorganisms:

Pseudomonas aeruginosa, Proteus species (indole-positive and indole-negative), *Escherichia coli* and *Klebsiella-Enterobacter-Serratia* species.

Clinical studies have shown GARAMYCIN Injectable to be effective in septicemia and serious infections of the central nervous system (meningitis), urinary tract, respiratory tract, gastrointestinal tract, skin and soft tissue (including burns).

Bacteriologic tests to determine the causative organisms and their susceptibility to gentamicin should be performed.

Bacterial resistance to gentamicin develops slowly in stepwise fashion; there have been no one-step mutations to high resistance.

In suspected or documented gram-negative sepsis, GARAMYCIN may be considered as initial therapy. The decision to continue therapy with this drug should be based on the results of susceptibility tests, the severity of the infection, and the important additional concepts contained in the Warning Box.

For suspected sepsis when the infecting organism is unknown, gentamicin may be administered in conjunction with a penicillin-type drug. Following identification of the organism and its susceptibility, appropriate antibiotic therapy should then be continued. In the neonate with suspected sepsis or staphylococcal pneumonia, a penicillin-type drug is also usually indicated as concomitant therapy with gentamicin.

GARAMYCIN Injectable has been shown to be effective in serious staphylococcal infections. It may be considered in those infections when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility testing and clinical judgment indicate its use.

CONTRAINDICATIONS A history of hypersensitivity to gentamicin is a contraindication to its use.

WARNINGS See Warning Box.

PRECAUTIONS Neuromuscular blockade and respiratory paralysis have been reported in the cat receiving high doses (40 mg./kg.) of gentamicin. The possibility of these phenomena occurring in man should be considered if gentamicin is administered to patients receiving neuromuscular blocking agents, such as succinylcholine and tubocurarine.

Treatment with gentamicin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy is indicated.

ADVERSE REACTIONS:

Nephrotoxicity: Adverse renal effects, as demonstrated by rising BUN, NPN, serum creatinine and oliguria, have been reported. They occur more frequently in patients with a history of renal impairment treated with larger than recommended dosage.

Neurotoxicity: Adverse effects on both vestibular and auditory branches of the eighth nerve have been reported in patients on high dosage and/or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss.

Numbness, skin tingling, muscle twitching, and convulsions have also been reported.

Note: The risk of toxic reactions is low in patients with normal renal function who do not receive GARAMYCIN Injectable at higher doses or for longer periods of time than recommended.

Other reported adverse reactions, possibly related to gentamicin, include increased serum transaminase (SGOT, SGPT), increased serum bilirubin, transient hepatomegaly, decreased serum calcium; splenomegaly, anemia, increased and decreased reticulocyte counts, granulocytopenia, agranulocytosis, thrombocytopenia, purpura; fever, rash, itching, urticaria, generalized burning, joint pain, laryngeal edema; nausea, vomiting, headache, increased salivation, lethargy and decreased appetite, weight loss, pulmonary fibrosis, hypotension and hypertension.

DOSAGE AND ADMINISTRATION

GARAMYCIN Injectable may be given intramuscula or intravenously.

For Intramuscular Administration:

Patients with normal renal function

Adults: The recommended dosage for GARAMYCIN Injectable for patients with serious infections and normal renal function is 3 mg./kg./da administered in three equal doses every 8 hours.

For patients weighing over 60 kg. (132 lb.), the usu dosage is 80 mg. (2 ml.) three times daily. For patien weighing 60 kg. (132 lb.) or less, the usual dosage is 60 mg. (1.5 ml.) three times daily.

In patients with life-threatening infections, dosage up to 5 mg./kg./day may be administered in three c four equal doses. This dosage should be reduced to 3 mg./kg./day as soon as clinically indicated.

In children and infants, the newborn, and patien with impaired renal function, dosage must be adjus in accordance with instructions set forth in the Package Insert.

For Intravenous Administration:

The intravenous administration of GARAMYCIN Injectable is recommended in those circumstances when the intramuscular route is not feasible (e.g., patients in shock, with hematologic disorders, with severe burns, or with reduced muscle mass).

For intravenous administration in adults, a single dose of GARAMYCIN Injectable may be diluted in or 200 ml. of sterile normal saline or in a sterile solu tion of dextrose 5% in water; in infants and children the volume of diluent should be less. The concentra tion of gentamicin in solution in both instances sho normally not exceed 1 mg./ml. (0.1%). The solutio infused over a period of one to two hours.

The recommended dose for intravenous admini tration is identical to that recommended for intramuscular use.

GARAMYCIN Injectable should not be physicall premixed with other drugs, but should be administ separately in accordance with the recommended r of administration and dosage schedule.

HOW SUPPLIED GARAMYCIN Injectable, 40 mg. per ml., is supplied in 2 ml. (80 mg.) multip dose vials and in 1.5 ml. (60 mg.) and 2 ml. (80 mg disposable syringes for parenteral administration.

Also available, GARAMYCIN Pediatric Injectabl 10 mg. per ml., supplied in 2 ml. (20 mg.) multiple dose vials for parenteral administration.

011 JUNE
AHFS Category 8.1

For more complete prescribing details, con Package Insert or Physicians' Desk Referen Schering literature is also available from yo Schering Representative or Professional Services Department, Schering Corporatio Kenilworth, New Jersey 07033.

Garamycin® I.M./I.V.
gentamicin sulfate 80mg./2ml.
injectable
40 mg./ml. Each ml. contains gentamicin sulfate equivalent to 40 mg. of gentamicin

*Due to susceptible organisms

SLS-5

Doctor, your office staff may have an acute case of cephalalgia.

If your office is still doing hand-to-hand billing, chances are it's giving your staff a real pain. And it's costing you nothing but money.

But SAFECOM, a SAFECO company, has an automated billing and insurance system that can cure it.

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Please give me the facts.

☐ Have your representative call me.
☐ Please send additional information.

Name _____

Person to contact _____

Address _____

City _____ State _____ Zip _____

Telephone _____

How many of your patients know what the B vitamins are?

But they do know what breads and cereals are.

The foods above have several nutrients in common. Among them are the vitamin B complex, necessary for healthy skin and a well-functioning nervous system. The B vitamins include thiamin (B_1), niacin and riboflavin (B_2). These foods are classified as the Bread & Cereal Group in the U.S. Department of Agriculture's Four Food Groups system.

Some physicians counsel patients in terms of nutrients. Which is easier for them to understand—foods or nutrients?

For attractive, color copies of the Four Food Groups guide for your patients, write: Dairy Council of California, Box 28F, Sacramento, CA 95825.

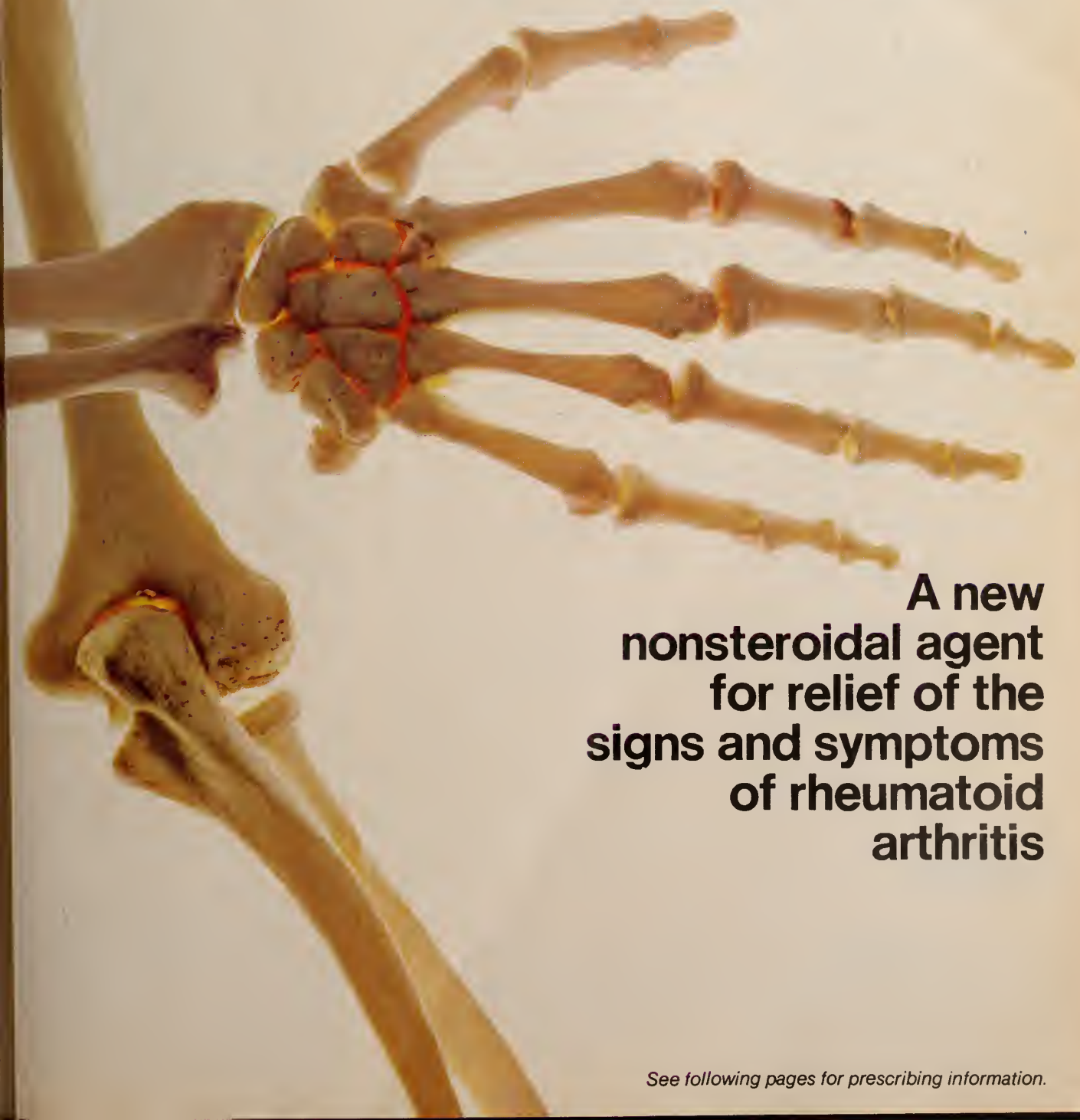
Dairy Council of California

The Four Food Groups—milk, meat, vegetables and fruits, breads and cereals—a practical guide to good nutrition.

New from
Lilly/Dista Research

NALFON®

fenoprofen calcium



A new nonsteroidal agent for relief of the signs and symptoms of rheumatoid arthritis

See following pages for prescribing information.

NALFON®
fenoprofen calcium

...reduces the pain and inflammation of rheumatoid arthritis* ...and it is well tolerated

New propionic acid derivative

NALFON® *(fenoprofen calcium)*
300-mg.† Pulvules®

- Relieves arthritic pain
- Reduces inflammation
- Improves function and mobility
- Well tolerated
- Chemically unrelated to aspirin, indomethacin, phenylbutazone, or corticosteroids

600472

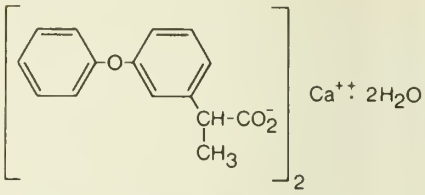
DISTA

*The safety and effectiveness of Nalfon have not been established in those rheumatoid arthritis patients who are designated by the American Rheumatism Association as Functional Class IV (largely or wholly incapacitated with patient bedridden or confined to wheelchair, permitting little or no self-care).

†Present as 345.9 mg. of the calcium salt of fenoprofen dihydrate equivalent to 300 mg fenoprofen

Description: Pulvules® Nalfon® (fenoprofen calcium, Dista) for oral administration contain fenoprofen calcium as the dihydrate in an amount equivalent to 300 mg. of fenoprofen. Nalfon is a nonsteroidal, anti-inflammatory drug. Chemically it is a propionic acid derivative.

The structural formula is as follows:



Calcium dl-2-(3-phenoxyphenyl) propionate dihydrate.

Nalfon is a white crystalline powder, soluble in U.S.P. ethanol (95%) to the extent of approximately 15 mg./ml. at 25 C°; slightly soluble in water, and insoluble in benzene.

The pKa of Nalfon is 4.5 at 25° C.

Clinical Pharmacology: Nalfon is a nonsteroidal, anti-inflammatory, anti-arthritic compound. In animal systems, it also shows analgesic and antipyretic activity. Its mode of action is unknown. In patients with rheumatoid arthritis, the anti-inflammatory action of Nalfon has been shown by a reduction in joint swelling, a reduction in pain, a reduction in the duration of morning stiffness, a reduction in disease activity as assessed by both the investigator and the patient, and by increased mobility as demonstrated by a reduction in the number of joints with limited motion. Its action is not mediated through the adrenal gland. There is no evidence that Nalfon alters the progressive course of the underlying disease.

To further demonstrate the anti-inflammatory activity of Nalfon in humans, the emergence and degree of erythemic response were measured in adult male volunteers exposed to ultraviolet irradiation. The effects of Nalfon, aspirin, and indomethacin were compared separately with those of placebo. All three drugs demonstrated anti-erythemic activity. The results in humans confirmed the anti-inflammatory activity found in animals.

Nalfon has been shown to inhibit prostaglandin synthetase isolated from bovine seminal vesicles. Reproduction studies in rats have shown Nalfon to be associated with prolonged labor and difficult parturition when given during late pregnancy. Evidence suggested that this may be due to decreased uterine contractility resulting from the inhibition of prostaglandin synthesis.

Under fasting conditions, Nalfon is rapidly absorbed, achieving peak plasma levels of 50 mcg. per ml. within two hours of oral administration of 600 mg. doses. Good dose proportionality was observed between 200 mg. and 600 mg. in fasting male volunteers. The plasma half-life is approximately 3 hours. Approximately 90% of a single oral dose is eliminated within 24 hours as fenoprofen glucuronide and 4′-hydroxyfenoprofen glucuronide, the major urinary metabolites of fenoprofen. Fenoprofen is highly bound (99%) to albumin.

The coadministration of aspirin decreases the biologic half-life of fenoprofen due to an increase in metabolic clearance which results in a greater amount of hydroxylated fenoprofen in the urine. Although the mechanism of interaction between fenoprofen and aspirin is not totally known, enzyme induction or displacement of fenoprofen from plasma albumin binding sites are possibilities. Chronic administration of phenobarbital, a known enzyme inducer, may be associated with a decrease in plasma half-life of fenoprofen. Clinical significance of these interactions is not known.

The concomitant administration of antacid (aluminum and magnesium hydroxide) does not interfere with absorption of Nalfon. Food ingestion decreases the rate and extent of absorption of Nalfon.

With single doses of Nalfon there is less suppression of collagen-induced platelet aggregation than with aspirin.

Fenoprofen shows anti-inflammatory effects in rodents by inhibiting the development of redness

and edema in acute inflammatory conditions and by reducing soft-tissue swelling and bone damage associated with chronic inflammation. It exhibits analgesic activity in rodents by inhibiting the writhing response in mice caused by the introduction of an irritant into the peritoneal cavity and by elevating pain thresholds to pressure in edematous hindpaws of rats. In rats made febrile by the subcutaneous administration of brewer's yeast, fenoprofen produces antipyretic action. These effects are characteristic of nonsteroidal, anti-inflammatory, antipyretic, analgesic drugs.

Indications and Usage: Nalfon® (fenoprofen calcium, Dista) is indicated for relief of the signs and symptoms of rheumatoid arthritis. It is indicated in the treatment of acute flares and in the long-term management of the disease. The safety and effectiveness of Nalfon have not been established in those rheumatoid arthritis patients who are designated by the American Rheumatism Association as Functional Class IV. (Incapacitated, largely or wholly bedridden, or confined to wheelchair; little or no self-care.) Improvement in patients treated with Nalfon for rheumatoid arthritis has been demonstrated by a reduction in joint swelling, a reduction in pain, a reduction in the duration of morning stiffness, a reduction in disease activity as assessed by both the investigator and the patient, and by increased mobility as demonstrated by a reduction in the number of joints with limited motion.

In clinical studies in patients with rheumatoid arthritis, Nalfon has been shown to be comparable to aspirin in controlling the aforementioned measures of disease activity but the frequency of the milder gastrointestinal adverse effects (nausea, dyspepsia) and tinnitus was less than in aspirin-treated patients. It is not known whether Nalfon causes less peptic ulceration than aspirin.

In some patients Nalfon has been used in combination with gold salts or corticosteroids. Studies have been inadequate to demonstrate whether Nalfon adds any improvement in patients maintained on gold salts or corticosteroids. Whether Nalfon could be used in conjunction with partially effective doses of corticosteroid for a "steroid-sparing" effect has not been adequately studied. The use of Nalfon in combination with salicylates is not recommended because there is no evidence to demonstrate that Nalfon would produce any additional effect beyond that produced by aspirin alone. Further, there is evidence that aspirin increases the rate of excretion of Nalfon.

There have been no studies in children; therefore the safety and effectiveness of Nalfon in children are unknown.

Contraindications: Nalfon is contraindicated in patients who have shown hypersensitivity to it.

Because the potential exists for cross sensitivity to aspirin and other nonsteroidal, anti-inflammatory drugs, Nalfon should not be given to patients in whom aspirin and other nonsteroidal, anti-inflammatory drugs induce the symptoms of asthma, rhinitis, or urticaria.

Warnings: Nalfon should be given under close supervision to patients with a history of upper gastro-intestinal tract disease and only after consulting the "ADVERSE REACTIONS" section. Gastro-intestinal bleeding, sometimes severe, has been reported in patients receiving Nalfon.

In patients with active peptic ulcer and active rheumatoid arthritis, attempts should be made to treat the arthritis with nonulcerogenic drugs, such as gold. If Nalfon must be given, the patient should be under close supervision for signs of ulcer perforation or severe gastrointestinal bleeding.

In subacute and chronic studies in rats, Nalfon caused interstitial nephritis, glomerulonephritis and renal papillary necrosis. These abnormalities were dose-related and began to appear at doses approximating the human dose. In chronic studies in monkeys interstitial nephritis also occurred following Nalfon administration. Although this was seen at doses considerably above the human dose, lower doses were not studied in this species. During the course of the clinical trials one patient developed renal failure and died with a diagnosis of septicemia, bilateral suppurative pyelonephritis and renal papillary necrosis. It is not known whether these events were drug-related. A few patients developed mild elevations of the BUN during Nalfon® (fenoprofen calcium, Dista) therapy. Since Nalfon is eliminated primarily by the kidney, the drug should not be administered to patients with significantly impaired renal function. It is desirable to perform periodic renal function tests in all patients receiving Nalfon.

Precautions: In chronic studies in rats, high doses of Nalfon caused elevation of serum transaminase and hepatocellular hypertrophy. In clinical trials, some patients developed elevation of serum transaminase, LDH, and alkaline phosphatase which persisted for some months, and usually, but not always, declined despite continuation of the drug. The significance of this is unknown. It is recommended that periodic liver function tests be performed in patients receiving Nalfon and that the drug be discontinued if abnormalities occur.

The safety of this drug in pregnancy and lactation has not been established and its use during these events is, therefore, not recommended. Reproduction studies have been performed in rats and rabbits. When fenoprofen was given to rats during pregnancy and continued to the time of labor, parturition was prolonged. Similar results have been found with other nonsteroidal, anti-inflammatory drugs which inhibit prostaglandin synthetase.

In-vitro studies have shown that fenoprofen, because of its affinity for albumin, may displace from their binding sites other drugs which are also albumin bound and may lead to drug interaction. Theoretically, fenoprofen, as well as other nonsteroidal, anti-inflammatory agents, could likewise be displaced. Patients receiving hydantoin, sulfonamides, or sulfonylureas should be observed for signs of toxicity to these drugs. In patients receiving coumarin-type anticoagulants, the addition of Nalfon to therapy could prolong the prothrombin time. Patients receiving both drugs should be under careful observation.

In patients receiving concomitant Nalfon-steroid therapy, any reduction of steroid dose should be gradual to avoid the possible complications of sudden steroid withdrawal.

Patients with initial low hemoglobin values who are receiving long term Nalfon therapy should have a hemoglobin determination at reasonable intervals.

Peripheral edema has been observed in some patients taking Nalfon; therefore, Nalfon should be used with caution in patients with compromised cardiac function.

Studies to date have not shown changes in the eye attributed to Nalfon administration. However, because of adverse eye findings in animal studies with some other nonsteroidal anti-inflammatory drugs, it is recommended that ophthalmologic studies be carried out within a reasonable period of time after starting chronic Nalfon therapy and at periodic intervals thereafter.

Since food decreases Nalfon blood levels, the drug should be given 30 minutes before or two hours after meals during the daytime.

When phenobarbital, which may enhance the metabolism of Nalfon, is added or withdrawn, Nalfon dosage adjustment may be required.

Caution should be exercised by patients whose activities require alertness if they experience central nervous system side effects from Nalfon.

Since the safety of Nalfon in patients with impaired hearing loss has not been established, these patients should have periodic tests of auditory function when chronic Nalfon therapy is given.

Nalfon decreases platelet aggregation and prolongs bleeding time. Patients who may be adversely affected by prolongation of the bleeding time should be carefully observed when Nalfon is administered.

Adverse Reactions: *Digestive System*

The most common type of adverse reaction concerned the gastro-intestinal system. Dyspepsia occurred most frequently, being observed in about one out of seven patients. Other adverse reactions in descending order of frequency were: constipation, nausea, vomiting, abdominal pain, anorexia, occult blood in the stool, diarrhea, flatulence, and dry mouth.

Three instances of peptic ulceration and/or gastro-intestinal hemorrhage that may have been due to the drug and four instances in which drug relationship was questionable were observed in 3,391 individuals to whom the drug was administered for periods of time ranging up to 165 weeks.

In less than 2% of patients the drug was discontinued because of adverse gastro-intestinal reactions.

Skin and Appendages

The most common adverse effect was pruritus which was seen in about one out of ten patients. Other adverse reactions were: rash, increased sweating, and urticaria.

In about 1% of patients Nalfon® (fenoprofen calcium, Dista) was discontinued due to an adverse effect related to the skin.

Nervous System

The most frequent adverse reaction observed was somnolence which occurred in about one out of seven patients. Other adverse effects which occurred less frequently were: dizziness, tremor, confusion, and insomnia.

Nalfon was discontinued in less than 0.2% of patients because of these side effects.

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The most common adverse reaction was tinnitus which was seen in about one out of ten patients. Other reactions observed in descending order of frequency were: blurred vision and decreased hearing.

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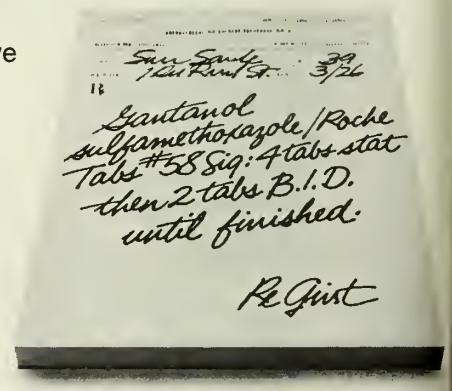

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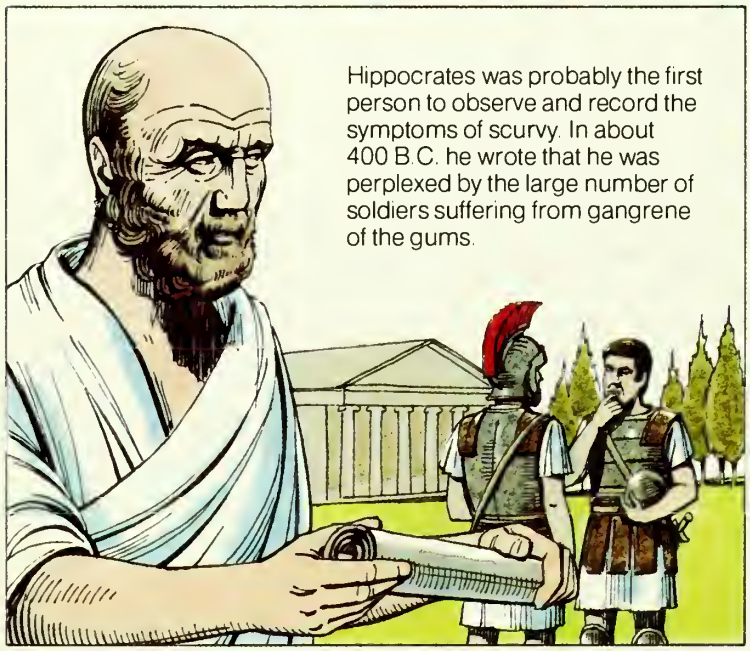

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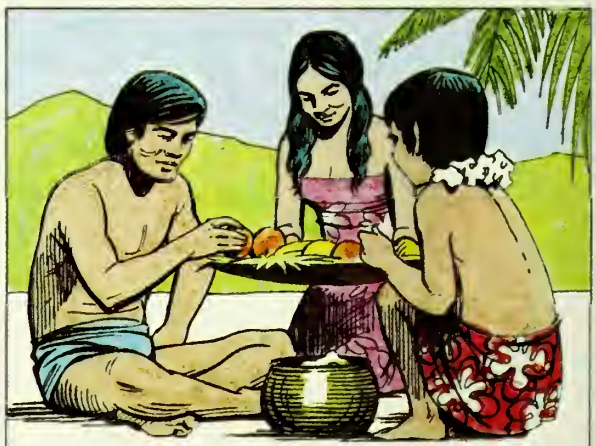

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THE WESTERN
Journal of Medicine

Percutaneous Radiofrequency Trigeminal Gangliolysis in the Treatment of Tic Douloureux

JOHN F. HOWE, MD; JOHN D. LOESER, MD, *and* RICHARD G. BLACK, MD, *Seattle*

The treatment of tic douloureux was dramatically altered in 1962 with the demonstration that carbamazepine (Tegretol®) alone or in combination with diphenylhydantoin sodium (Dilantin®) was effective in controlling the painful paroxysms. However, 30 percent of the patients so treated have not been successfully managed and some type of surgical therapy is required to control their pain. A wide variety of surgical alternatives are available but they all trade a sensory deficit for pain relief and have a significant risk of morbidity and mortality.

Experience with percutaneous radiofrequency trigeminal gangliolysis has indicated that this new technique is capable of producing lasting relief of tic douloureux in as many as 95 percent of the patients. To date there have been no deaths from this procedure and a very low incidence of minor complications. It achieves this high success rate at the expense of only partial sensory deficits restricted to a circumscribed area of the face. No other surgical alternative carries such a high long-term success rate with a low complication rate. We believe that percutaneous radiofrequency trigeminal gangliolysis has become the surgical treatment of choice for tic douloureux.

TIC DOULOUREUX is a paroxysmal facial pain of unknown cause and pathophysiology. It has the following characteristics: (1) Intermittent, sharp, lancinating electric shock-like pains limited to the trigeminal nerve distribution. Rarely, the pain is perceived in the territory of the nervus intermedius or glossopharyngeal nerve. (2) There are pain-free intervals. (3) The pain is always unilateral. (4) The pain is precipitated by nonnoxious stimulation in a repeatedly demonstrable trigger area which is always ipsilateral to the pain. (5) Results of neurologic examination are usually normal but may show mild sensory changes in the area in which the pain is perceived. (6) The frequency of paroxysms is very

From the Departments of Neurological Surgery (Drs. Howe and Loeser); and the Department of Anesthesiology (Dr. Black), University of Washington School of Medicine.

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Submitted October 6, 1975.

Reprint requests to John D. Loeser, MD, Department of Neurological Surgery, University of Washington School of Medicine RI-20, Seattle, WA 98195.

variable, occurring often in clusters which last days, weeks or months, but sometimes with spontaneous remissions between flurries of attacks.

Rothman estimates that there are 7,000 new cases of tic douloureux each year in the United States.[1] Approximately 70 percent of these patients can be successfully controlled by using carbamazepine (Tegretol®).[2-6] By adding diphenylhydantoin sodium (Dilantin®) to Tegretol another 10 to 15 percent can be controlled.[5] Serious side effects can require cessation of Tegretol administration in 5 to 19 percent of the patients taking this drug (skin rash, leukopenia, thrombocytopenia, abnormal liver function tests).[3,5,6] Consequently, in 30 percent of the patients with tic douloureux, pain will not be controlled by medication. No other drugs have been reliably effective for the control of the pain of tic douloureux.

A wide variety of effective curative and palliative surgical procedures designed to damage the trigeminal nerve exist. The literature is replete with advocates of every conceivable technique for traumatizing or excising the trigeminal system from the periphery to the brain stem. These procedures are summarized in Table 1. They have in common the goal of producing some sensory deficit in the painful region without producing other neurological deficits, morbidity or mortality. Since several of the complications of surgical operation for tic douloureux are directly related to the amount of sensory deficit produced (anesthesia dolorosa, neuroparalytic keratitis, paresthesia), it seems to be of value to limit the sensory deficit to the minimum necessary to achieve long-lasting pain relief.

We present here our initial experience with percutaneous radiofrequency trigeminal ganglionolysis. This procedure offers the ability to limit the sensory deficit to a preselected region of the face and to just the "pain modality"; hypalgesia or analgesia without anesthesia is produced. We have used with slight modifications the technique

TABLE 1.—*Destructive Procedures for Tic Douloureux*

Procedure	*Effectiveness*		*Sensory Deficits*	*Complications*
	Immediate (Percent)	*Long-term (Percent)*		
Peripheral neurectomy	79-100	0-14*	Anesthesia and analgesia	Mortality 0; minor and rare, anesthesia dolorosa reported, incidence unknown
Alcohol injection				
Nerve[9,13]	80-90	0-10†	Variable, usually anesthesia and analgesia	Spread of alcohol to other cranial nerves and brain stem can occur, mortalities reported
Ganglion[8,9,11-15]	97	70	Anesthesia and analgesia	Mortality 0-1%; corneal anesthesia 15-44%; keratitis 15-44%; anesthesia dolorosa 5-12%; spread to other cranial nerves and brain stem—incidence not documented
Intracranial				
Middle fossa[7] trigeminal rhizotomy	99	90	Anesthesia and analgesia	Mortality 0.4-3.4%; keratitis 5%; anesthesia dolorosa 10%; other cranial nerves 2%
Middle fossa[7] ganglion percussion	98	77	Variable, hypalgesia and hypesthesia	Mortality 1-2%; keratitis 0; anesthesia dolorosa 0; other cranial nerves 3%
Posterior fossa[7] trigeminal rhizotomy	100	70-80	Analgesia and anesthesia	Mortality 2.0-4.5%; keratitis 1-2%; anesthesia dolorosa 2%; other cranial nerves 2%
Medullary[7] trigeminal tractotomy	89	80	Analgesia without anesthesia	Mortality 1%; keratitis 0.8%; anesthesia dolorosa 0.4%; ataxia 6%; variable lower cranial nerve palsies
Radiofrequency[16-18] trigeminal gangliolysis	99	80-90	Analgesia without anesthesia	Mortality 0; keratitis 0.6%; anesthesia dolorosa 1.3%; other cranial nerves 0

*Virtually 100 percent have return of pain within one year.
†Virtually 100 percent recurrence with 8 to 16 months.

described by Sweet and Wepsic.[7,16] Their original work was based upon Kirschner's diathermic coagulation of the Gasserian ganglion begun in 1925. The technique as then practiced made use of general anesthesia and produced a significant number of severe complications.[7] By 1972, Thiry had refined the procedure by making partial lesions.[19] At this point the technique had similar complications and success rates to the open surgical and anesthetic neurodestructive procedures. Schürmann and co-workers improved the technique by using neuroleptic analgesia, allowing them to monitor the sensory deficit produced during the course of the operation.[20] Sweet and Wepsic's modifications included electrical stimulation through the needle to verify the location of the needle tip before making the lesion, and the use of radiofrequency current to produce a thermally generated lesion which was much more controllable than diathermy electrical coagulation. In addition, temperature monitoring with a thermistor was used to prevent sudden overheating and gassing at the electrode tip.

Technique

The objective of this technique is to limit the lesion to just those fibers of the trigeminal nerve that are involved in the pain. This is accomplished by percutaneously introducing a needle through the foramen ovale into the Gasserian ganglion under fluoroscopic control. Since this part of the procedure can be painful, brief neuroleptic anesthesia is useful; we now use premedication with fentanyl citrate and droperidol (Innovar®) and intermittent inhalation of nitrous oxide and oxygen (N_2O-O_2) by mask. Once the needle is in the ganglion, low voltage, 60 hertz stimulation is used to produce paresthesiae which are perceived by the patient in the peripheral distribution of the fibers among which the electrode tip is lying. The patient reports where he feels the paresthesiae and the electrode is adjusted to produce the tingling sensation in the area where the patient has previously perceived his pain. Low frequency (5 to 10 Hz) stimulation is then used to ascertain that the motor division is not close to the electrode tip. When the needle is adjacent to the appropriate fibers the radiofrequency current is turned on and the temperature of the tip is gradually raised to 70°C. If the temperature is allowed to rise very slowly (over a three minute period) the patient may not feel significant pain; however, some patients do find the thermal coagulation of the ganglion painful and, for this reason, brief neuroleptic anesthesia with nitrous oxide is useful. The desired electrode temperature is maintained for 90 seconds to produce a permanent lesion within the ganglion. The patient is then awakened from the anesthetic and examined for sensory deficits. If more deficit is required the lesion can be enlarged by reheating to 80°C for 90 seconds. The needle can also be shifted to a more suitable location and another lesion produced. In this way the location and size of the lesion can be controlled and unwanted neurologic deficits avoided.

The technique of percutaneous radiofrequency trigeminal gangliolysis takes advantage of the fact that the unmyelinated and thinly myelinated fibers are very much more sensitive to heating and are damaged preferentially during gangliolysis. All available clinical and experimental evidence supports the concept that these Aδ and C fibers are the only sources of peripheral nociceptive information; the patient develops a sensory deficit limited only to the "pain modality."[21] Touch and proprioceptive modalities are left intact. At the end of the procedure the tic pain is eliminated. The sensory deficit is discretely localized and is restricted primarily to the perception of pain and temperature.

Results

This report includes our initial group of 32 consecutive patients with tic douloureux, drawn from the University of Washington Affiliated Hospitals. All procedures were done between January 1973 and May 1975. The average age of our patients was 61, ranging from 31 to 77. There were 19 women and 13 men. They had an average duration of symptoms of 7.7 years, ranging from one month to 25 years. In many of the patients there was a past history of remission, either spontaneous or induced by medical or surgical therapy. Seventeen of the patients had been treated earlier with a neurodestructive procedure, the most common being alcohol block of the nerve or Gasserian ganglion.

Of our 32 patients, 31 had been treated with Tegretol, one was treated with Dilantin alone. Of the 31 who received Tegretol, 12 received Dilantin in addition. Of these 31 patients, in 9 there was no relief at all from either of these drugs, in 12 there was partial or incomplete relief and in 5 others there was control of pain for several months to several years; then it "broke

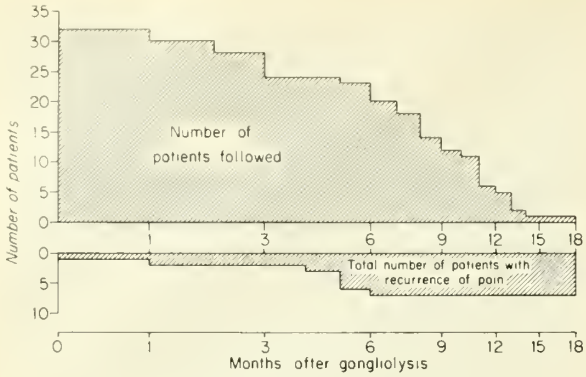

Figure 1.—Gangliolysis for tic douloureux.

through" and no relief was achieved even when the drugs were carried to toxic levels. These 26 patients underwent gangliolysis because of poor control of pain. In an additional five patients there was control with Tegretol but toxic symptoms developed that required withdrawal of the drug. All of our 32 patients were examined one month postoperatively and at regular intervals thereafter and were then interviewed in June 1975 by telephone or in person. Therefore, we have follow-up periods ranging from 1 to 17 months.

In only one of the 32 patients was there failure to achieve any relief of pain. Most of the others were pain-free from the time of the gangliolysis, although a few experienced brief attacks of pain in the immediate postoperative hours before achieving lasting relief.

Six patients had return of their original tic pain during the follow-up period. In two pain recurred within one month and in one each at four, five, seven and eight months after gangliolysis (Figure 1). Of the entire series, followed until June 1975, this represents a 21 percent recurrence of pain. Of the seven patients with pain recurrence, five had had earlier neurodestructive procedures carried out involving the trigeminal ganglion. This may indicate that either their tic was more refractory to control by any method or that the earlier procedure itself decreased the ability of the gangliolysis to achieve the therapeutic effect. It was observed during gangliolysis that in those patients in whom earlier procedures affecting the Gasserian ganglion had been carried out, it was much more difficult to produce paresthesiae in the desired location and much more difficult to achieve an adequate lesion at the time of gangliolysis. However, in 12 of the patients who had had earlier neurodestructive procedures, long-lasting pain relief was achieved following gangliolysis. We were unable to identify pregangliolysis or postgangliolysis features of these patients which would enable us to predict in whom long-term success would be achieved and in whom there would be a relapse after gangliolysis.

Subsequent management of these seven patients involved a return to preoperative status in three, requiring acceptance of toxic side-effects or partial control, or both. Two of the patients in whom initially there was no benefit from Tegretol are adequately managed on reasonable doses of this drug following the gangliolysis. One patient finds the recurrent pain mild enough that he prefers not to take medication. In one other patient who had only minor pain symptoms, severe endogenous depression developed and his pain could not be adequately managed. In this series of 32, the condition was made no worse by the gangliolysis.

We were able to produce a sensory deficit in some portion of the painful region in all but one patient in whom, oddly enough, there was complete relief of first and second division tic douloureux by a lesion that was restricted to the third division. The lesion produced by gangliolysis extended to some degree into an adjacent division not involved by pain in 16 patients. However, the extended lesion involved only a portion of additional adjacent divisions, and was in no case detrimental to the patient's well-being. The sensory deficit was limited to pain and temperature perception in 22 of the 32 patients. In all but one of the remainder some degree of touch sensation was preserved.

Decrease in size and density of the sensory deficit occurred in most patients regardless of the long-term pain relief and some patients lost essentially all of their sensory deficit even though pain relief persisted.

In no case was a neurologic deficit produced outside the trigeminal nerve. Paresis of the ipsilateral muscles of mastication developed in nine patients but was symptomatic in just one patient with a earlier history of temporomandibular joint arthritis. No permanent impairment of jaw or masticatory function developed in any patient as a result of this procedure. When paresis of muscles of mastication was produced, it was invariably transient. Corneal anesthesia developed in four patients with return of sensation in two of these patients. In no patient did significant corneal pathology develop during the follow-up period.

In six of the 32 patients paresthesiae developed in the trigeminal distribution, but in no patient were they reported as being painful. Anesthesia dolorosa did not develop in any patient. There were no deaths, no infections and no other medical complications as a result of gangliolysis. One patient complained of transient tinnitus and ear fullness that was attributed to tensor veli palatini dysfunction. It was successfully treated with decongestant medications.

Discussion

Of 32 patients in whom percutaneous radiofrequency trigeminal gangliolysis was done, there was initial relief of pain in all but one and in only 21 percent was there recurrence. There was no mortality, and no neurologic deficit outside of the trigeminal nerve. Preservation of some touch sensation was present in 30 of the 31 patients. Corneal anesthesia was present in four patients, two of whom regained their sensation, and in no patient did keratitis develop.

Our experience is similar to that reported in the larger series of gangliolyses by Sweet and Wepsic, Nugent and Berry, and Onofrio.[16-18] Sweet and Wepsic treated 214 patients with tic douloureux and in those with follow-up periods ranging from two and a half to six years there was a 22 percent relapse rate.[16] By repeating the procedure in the 33 patients who had relapses, up to six times, they were able to achieve an overall success rate of 97 percent.

Nugent and Berry treated 65 patients, with 1 to 41 months of follow-up. They had an 11 percent recurrence rate and in all but one of these patients successful management was achieved by repeating the procedure.[17]

Onofrio reported 135 patients with tic douloureux with a recurrence rate of 15 percent occurring two weeks to 14 months postoperatively.[18] In these 446 patients in whom radiofrequency gangliolysis was done, the success rate varies from 78 to 90 percent with follow-up ranging up to six years. By repeating the procedure the success rate is in the range of 90 to 95 percent. In the combined experience there was no mortality and in only one patient did transient neurologic deficit develop outside the trigeminal system. At least partial touch sensation was preserved in the analgesic zone in about 90 percent of the patients. Keratitis developed in 0.6 percent of the cases and anesthesia dolorosa in 1.3 percent of the cases.

These results can be contrasted with those obtained by using various surgical and neurolytic injections as reported in several large series. As shown in Table 1, percutaneous radiofrequency trigeminal gangliolysis offers a higher success rate and a lower complication rate than any other currently available procedure.

Trigeminal peripheral neurectomy is safe, having a low incidence of minor complications, but must be considered temporizing since there is essentially a 100 percent recurrence rate within one and a half years. Alcohol injections of the peripheral nerves fall into the same category. Alcohol injection of the ganglion can have long-term effectiveness, and the incidence of complications can be very small when meticulously carried out by experienced operators. However, injection of the ganglion carries a notoriously high incidence of severe complications and a very low success rate on repeat injections. It is very difficult to control the extent of the lesion produced, and this procedure seems to have no advantage when contrasted with percutaneous radiofrequency gangliolysis. Middle fossa trigeminal rhizotomy has been considered among the safest and the most definitive procedures and has a high chance of initial control of symptoms; yet it carries at least a 10 percent recurrence rate and about a 1 percent mortality. Total sensory deficit is common and is associated with a 50 percent rate of postoperative paresthesiae and a 5 percent rate of anesthesia dolorosa.[13] Keratitis is reported in at least 1 percent of the patients and facial nerve paralysis has been reported in 18 percent of the patients, although it is permanent in a smaller group.[7] All of the complications of intracranial surgical operation can follow this operation.

Jannetta has recently claimed that most cases of tic douloureux are due to compression of the trigeminal root by an aberrant blood vessel.[22] He advocates isolating the offending vessel from the nerve root by a small nylon sponge inserted via a posterior fossa craniectomy under general anesthesia. The long-term efficacy, morbidity and mortality of this procedure is not established; it does offer the promise of pain relief without any sensory loss.

It is obvious that none of the established surgical procedures can offer the combination of low morbidity and mortality with high success rate that can be achieved with percutaneous radiofrequency trigeminal gangliolysis. The advantages

of this procedure are: (1) high rate of therapeutic effectiveness, which can be made about 95 percent by repeating the procedure; (2) ability to preserve touch sensation in regions that are analgesic; (3) zero mortality; (4) virtually zero incidence of neurologic deficit outside the trigeminal system, and (5) low incidence of associated complications.

If we assume that in 70 percent of all patients with tic douloureux adequate control of pain can be achieved with Tegretol, and that of those in whom it is not controlled with Tegretol, 80 to 85 percent will have a good result with a single gangliolysis, 94 percent of such patients can be successfully treated by either drugs or a relatively inexpensive and safe operative procedure. Gangliolysis can be repeated if not initially successful and can approximate a 98 percent success rate in the treatment of what is surely one of the most painful afflictions of man. This success rate can be achieved with essentially no incidence of mortality and a very low incidence of morbidity and only partial sensory loss. For these reasons, we believe that percutaneous radiofrequency trigeminal gangliolysis has become the treatment of choice for tic douloureux not responsive to Tegretol or Dilantin.

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Toxigenic Escherichia Coli and Childhood Diarrhea

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Stool specimens were examined from 40 children with diarrhea who were under three years of age to determine the incidence of enterotoxigenic Escherichia coli in endemic diarrhea. Heat-labile E. coli enterotoxin was assayed in the very sensitive and reproducible cultured adrenal tumor cell system. Toxigenic E. coli were isolated from only one stool specimen and in this case infection with Shigella dysenteriae was also present. None of the eight classic enteropathogenic E. coli isolates were positive in the adrenal assay. This study suggests that heat-labile enterotoxin-producing E. coli are not an important cause of endemic childhood diarrhea in Southern California.

ACUTE DIARRHEA is a common worldwide problem and is the largest single cause of death and loss of productivity in underdeveloped nations.[1] In the past few years enterotoxigenic Escherichia coli have been implicated as a cause of cholera-like diarrhea in India and in "Travelers' Diarrhea" among American students in Mexico.[2-4] There is also some evidence that these organisms may be the cause of diarrhea in Chicago children, but not in children from Honolulu.[5,6] In addition, the role of classic "enteropathogenic" serotypes in diarrheal disease is in question. For example, enterotoxigenic strains of E. coli were recently isolated from 10 of 59 Apache children with diarrhea but none of the 64 classic enteropathogenic serotypes of E. coli found were shown to be toxigenic by assay in the standard ileal-loop model.[7]

Recently it has been shown that cultured adrenal tumor cells become spherical and produce large quantities of steroids when exposed to heat-labile E. coli enterotoxin.[8,9] This tissue culture assay system is extremely sensitive, easily reproducible and highly specific for heat-labile enterotoxin.[7,10,11] In the present study the cultured adrenal cell system was used to determine the role of enterotoxigenic E. coli in endemic diarrheal disease among children in Orange County, California.

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This investigation was conducted by D.H.M. during his graduate studies completed at California State University, Long Beach, in June, 1975.

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Materials and Methods

Patients and Clinical Data. In the summer of 1974, 40 consecutive children 3 years of age or under with acute diarrhea, who were examined in clinics at Orange County Medical Center or the Orange County Health Department, or admitted to hospital at Orange County Medical Center were studied. A summary of acute symptoms, past history, physical findings and laboratory data was derived from review of clinic or hospital records.

Stool Samples and Bacteriologic Methods. Stool or rectal swab specimens were streaked directly on MacConkey, xylose-lysine-desoxycholate (XLD) and Hektoen agar plates and incubated overnight. Selenite broth was inoculated and preincubated before subculturing in order to enhance recovery of Salmonella. Lactose-negative colonies were picked for subculture and identified by standard biochemical and serologic methods.

For further study of E. coli, three or four individual lactose-fermenting colonies were each subcultured to nutrient agar slants, incubated overnight, then stored at 4°C. Of these isolates, 115 were identified by standard biochemical techniques to be E. coli and were used for further serologic and toxigenicity studies. One E. coli isolate from each stool specimen was serogrouped for somatic antigen by the tube agglutination method of Edwards and Ewing[12] using a set of 134 rabbit "O" antisera supplied by the Center for Disease Control, Atlanta, Georgia. All E. coli isolates from the 40 specimens were tested for enterotoxin production.

Adrenal Tumor Cell Assay for Identification of Enterotoxigenic E. Coli. E. coli isolates were assayed for heat-labile enterotoxin production by a previously described adrenal tumor cell assay system.[9] Adrenal monolayer morphology was observed under a phase-contrast microscope (Nikon MS) and steroid production was measured fluorometrically.[13] Each E. coli isolate was grown in a shaking incubator overnight at pH 8.5 in a broth containing 2.0 percent casamino acids (Difco), 0.6 percent yeast extract (Difco) and 0.25 percent glucose, conditions shown to produce a high yield of enterotoxin from positive control isolates (Mundell DH, Anselmo CR and Wishnow RM, unpublished observation). The cells were removed by centrifugation (12,000 times gravity for 15 minutes) and the supernatant filtered through a Millipore® filter (0.22 micron). Broth culture filtrate (0.2 ml) was added to confluent monolayers in 60 by 15 mm tissue culture dishes (Falcon) containing 1.8 ml of Eagle's minimum essential medium (Gibco). After 24 hours of incubation at 37°C cell morphology and steroidogenesis were assayed with excellent reproducibility. Both positive and negative control E. coli were included with each assay group.

TABLE 1.—*Clinical Data in 40 Cases of Acute Diarrhea in Orange County Children*

	Patients	
	Number	*Percentages of Total*
Admitted to hospital	20	50.0
Age (years)		
<1	27	67.5
1-3	13	32.5
Fever (temperature, °C)		
≥39	10	25.0
37.5 to 38.9	9	22.5
<37.5	14	35.0
Not recorded	7	17.5
Gastrointestinal symptoms		
Mild	6	15.0
Moderate to severe*	34	85.0
Duration of diarrhea (days)		
≥7	12	30.0
3-6	12	30.0
<3	16	40.0
Travel to Mexico	6	15.0
Antibiotic therapy before onset of diarrhea	5	12.5

*Based on the presence of one or a combination of the following conditions: four stools per day, bloody stool and vomiting.

TABLE 2.—*Bacteriologic Findings in 40 Cases of Acute Diarrhea in Orange County Children*

Pathogenic Organism	*Number of Patients*	*Number of Patients with Enterotoxigenic Escherichia Coli*
Shigella dysenteriae	1	1
Shigella flexneri	2	..
Enteropathogenic Escherichia coli		
020	1	..
026	2	..
055	2	..
086	1	..
0119	1	..
0126	1	..
None of above isolated	29	..
TOTALS	40	1

Results

Clinical Findings. The clinical features of the diarrheal illness in these children are shown in Table 1. Of the 40 children in this study, 27 were less than 1 year of age and half of the children required admission to hospital. In 34 of the 40 children there were moderate or severe gastro-

intestinal symptoms (more than four stools a day with or without vomiting). In approximately 10 percent of the children in this study, bloody diarrhea was present. Half of the children in this study had initial temperatures greater than 37.5°C (99.5°F) and 25 percent had temperatures of 39°C (102.2°F) or more. It is interesting to note that six of these children had recently traveled to Mexico. Five of the patients received antibiotics before the first stool culture was made.

Bacteriologic Results. The complete bacteriologic results from this study are shown in Table 2. From this group of 40 children with diarrhea, bacterial pathogens were isolated from 12 (30 percent). Two of the children were infected with Shigella flexneri and one with Shigella dysenteriae. Classic "enteropathogenic" serotypes of E. coli were isolated from specimens of eight patients. However, none of these strains produced heat-labile enterotoxin.

The stool specimen from only one infant contained E. coli that proved to be enterotoxigenic. This infant had recently returned from Mexico and was also infected with Shigella dysenteriae. It is of interest that three of the E. coli isolates from this patient were E. coli serogroup 078 but only two of the three were enterotoxigenic.

In addition to E. coli isolates, strains of Klebsiella, Citrobacter and Proteus species isolated from these patients were also tested for toxin production; none of these isolates were positive in the adrenal tumor cell system.

Discussion

The purpose of this investigation was to determine the applicability of the adrenal cell culture system to routine study of stool specimens, and to establish the incidence of toxigenic E. coli in endemic diarrhea among infants and young children in Orange County, California. Gorbach and Khurana, using an infant rabbit gut assay, reported the isolation of toxigenic E. coli from 83 percent of 29 children admitted to hospital in Cook County Hospital, Chicago, with acute diarrhea.[5] Sack and co-workers recently reported the isolation of toxigenic E. coli from 18 percent of 59 Apache children admitted to hospital with acute diarrhea. In contrast, toxigenic strains of E. coli do not appear to be a major factor in endemic diarrhea in Southern California since in only one of 40 children with diarrhea did a specimen yield a toxin-producing E. coli strain. Furthermore, this infant was also infected with Shigella dysenteriae. It seems likely that both pathogens were acquired on a recent visit to northern Mexico. In this patient, all three E. coli isolates were of serogroup 078 and two of the three isolates were positive in the adrenal tumor cell assay system.

On the other hand, there is considerable evidence that traveler's diarrhea is caused by toxigenic E. coli.[4,14] A recent report shows that of 133 United States students newly arrived in Mexico, diarrhea developed in 29 percent.[4] Heat-labile enterotoxin-producing E. coli were isolated from 72 percent of the students with diarrhea.

In the present study, E. coli isolates were screened for production of heat-labile enterotoxin in the cultured adrenal cell system soon after initial isolation in order to avoid the possibility that enterotoxin production was determined by a labile plasmid. The assay depends upon enterotoxin activation of adrenal adenylate cyclase followed by an alteration of monolayer morphology and steroidogenesis.[9] The change from flattened to spherical-shaped cells appears to be related to increased intracellular adenosine 3′-5′-cyclic monophosphate concentration rather than steroidogenesis, and can easily be observed under phase contrast microscopy.[15] This morphologic change has been used as a screening test for toxigenic E. coli with excellent correlation with the ileal loop assay.[7,8] In addition, we have shown excellent agreement between the results of the following assay systems for the detection of heat-labile E. coli enterotoxin: ileal loop, vascular permeability, adrenal morphology and steroidogenesis (Evans DJ, Evans DG, Wishnow RM, unpublished observation). In the adrenal cell assay system used for the present studies in Orange County children the final dilution of culture filtrate was 1:10. Other investigators have used a similar concentration of culture filtrate in this sensitive assay.[7,8] It is unlikely that this concentration missed any toxigenic strains of E. coli because the adrenal assay will detect heat-labile enterotoxin in a 1:40 or greater dilution from positive control strains (Evans DJ, Evans DG, Wishnow RM, unpublished observation).

In this study we did not assay heat-stable enterotoxin production or invasiveness of the E. coli isolates. The role of invasive E. coli or E. coli strains producing only the heat-stable enterotoxin in diarrhea in the United States is still unknown. Only five patients were given antibiotics before the first stool examination; therefore it is

unlikely that antibiotic therapy significantly reduced the incidence of enterotoxigenic E. coli isolates. Since this study was carried out in the summer it is possible that newly described viruses such as the "reovirus-like" agent or Norwalk agent may have been responsible for a significant number of the cases of undiagnosed enterocolitis.[17-19]

Our study confirms previous reports that classic enteropathogenic serotypes frequently give negative results when assayed for E. coli enterotoxin. Eight of the 40 stool specimens did contain enteropathogenic organisms but these isolates were all enterotoxin-negative in the adrenal cell assay system. Results of this study as well as of several previous investigations suggest that routine serotyping of E. coli isolates from endemic diarrhea is of limited value.[4,7] Clinical laboratories that maintain continuous cell lines for diagnostic virology have the capability to maintain Y-1 adrenal tumor cells in serum supplemented Eagle's minimum essential medium. Such laboratories should consider replacing serotyping with the adrenal tumor cell assay system.

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Airborne Bacterial Contamination of Operative Wounds

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Both the numbers and species of airborne bacteria were studied during 263 surgical procedures. The numbers of bacteria isolated were reduced by 95 percent in a horizontal laminar flow room compared with a conventional room and a further 4 percent reduction occurred when a suction-mask system was used. The species of bacteria isolated differed notably at the operative site where a slit sampler was used, as compared with the instrument table and the periphery of the room where settling plates were used. Studies done during simulated surgical operation suggested that light fixtures, pass-through doors, floor contamination and the draped patient were not important sources of airborne contamination in this horizontal laminar flow system. The exact role of airborne bacterial contamination of operative wounds in the development of clinical wound infections is still unknown. Therefore, installation of laminar flow systems must be considered unnecessary at this time.

THE CONTROL of operative wound infections is a complex problem. Some of the proposed factors involved include airborne contamination,[1] anatomic site of the surgical wound,[2-4] amount of devitalized tissue, hematoma formation, implanted prosthetic material, use of antibiotics,[5-7] host resistance, glove and gown failure,[8] length of the operative procedure,[9] bacteremias of the genitourinary tract,[10] pharyngeal or respiratory origins[9,11] and levels of host resistance.

The sources of airborne bacterial contamination in the operating room are multiple. Airborne bacteria may arise from desquamation of the skin from the operative team or the patient,[2,9,12] or from their respiratory trees,[9] from fomites and from horizontal surfaces such as the floor. These sources may be affected by the position and clothing of the operating personnel;[13] by movement of personnel; by talking; by the type of air current, air exchange and air filtration in the operating suite,[1,2,14,15] and by the use of ultraviolet light.[16] The relative importance of airborne contamination in operative wound infections has been difficult to establish, but anything that would decrease the potential hazard from this and other sources would be beneficial.

In this prospective study, airborne bacteria in

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a horizontal laminar flow system and in a horizontal laminar flow system with a suction-hood aspiration system were compared with those in a conventional operating room. Sampling was done at the operative wound site using a slit sampler and from various locations in the operating room using settling plates. The numbers and species of bacteria were then compared. Also studied were the effects on airborne bacteria of (1) movement of operative team and of the patient in a horizontal laminar flow unit and (2) movement of light fixtures and pass-through doors in a horizontal laminar flow room.

Data were collected at a large community hospital from June 1971 to October 1974.

Methods and Materials

Bacteriological monitoring was done at the wound site in 123 operative or simulated operative procedures utilizing a Casella Slit Sampler connected by a 1-inch diameter tube attached to the sterile drapes adjacent to the operative site. This slit sampler aspirated 1 cubic foot of air per minute from the atmosphere at the operative site. This air impinged a rotating culture plate containing blood agar media (Mueller-Minton). Following exposure, the culture plate was incubated at 37°C and the resulting bacterial colonies were counted and identified. Data were converted to the mean number of bacteria per cubic foot per minute. Only aerobic cultures were done. Slit sampler monitoring was done for at least one hour in all but four cases and, henceforth, will be referred to as operative site monitoring.

Bacteriological monitoring was also done utilizing three settling plates on 148 other operative procedures. One plate was positioned at the operative instrument table. Another was positioned near the hallway door adjacent to the anesthesiologist but outside of the laminar flow enclosure. The third plate was positioned against the outer wall of the operative suite and was also outside the laminar flow unit.

During 88 surgical procedures, simultaneous operative site and settling plate monitoring was done. In 140 operative procedures, settling plate monitoring alone was done. Operative site monitoring alone was done in 35 simulated operative procedures. Two separate studies were carried out.

TABLE 1.—(Study I) *Comparison of numbers of bacteria isolated in a conventional operating room, a laminar flow room and a laminar flow room with a suction-hood system*

Group	*I*	*II*	*III*
No. of cases	18	50	27
Mean bacteria/cubic ft./minute	3.74	0.18	0.05

TABLE 2.—(Study I) *Comparison of numbers of bacteria in a conventional operating room with a laminar flow room and comparison of a laminar flow system with conventional masks with a laminar flow system with a suction-hood system*

Group	*I vs. II*	*II vs. III*
Percent difference in mean bacteria/cubic ft./minute	95% reduction	72% reduction
Significance level, 2 tailed T-test	P 0.001	P 0.05

TABLE 3.—(Study I) *Comparisons of numbers of bacteria during total knee operation (Group IV), conventional orthopedic procedures (Group V) and with a control (no patient) group (Group VI)*

Group	*IV*	*V*	*VI*
No. of cases	5	7	10
Mean bacteria/cubic ft./minute	0.04	0.45	0

STUDY I

In this study, the numbers and species of bacteria isolated in a conventional operating room were compared with bacteria isolated in a horizontal laminar flow room and horizontal laminar flow with an added suction-hood system.

Group I—In 18 cases, monitoring was done during operative procedures in a conventional operating room (ten air changes per hour). These included a variety of surgical procedures carried out by different surgical teams and in which gowning, draping and team position varied.

All subsequent studies were done in an oper-

TABLE 4.—(Study I) *Species of bacteria isolated during total hip replacement with conventional masks (Group II) and with a suction-hood system (Group III)*

	No. of Cases	*Total Colonies*	*Bacillus Subtilis (percent)*	*Staphylococcus Epidermidis (percent)*	*Staphylococcus Aureus (percent)*	*Neisseria (percent)*	*Gram-Rods (percent)*	*Miscellaneous (percent)*
Group II	50	949	40.4	35.6	1.2	11.2	.4	11.2
Group III	27	133	19.6	34.6	0	0	0	46.8 (Sarcina 36.1)

ating room equipped with a horizontal laminar flow system utilizing a high efficiency particulate air (HEPA) filter. This provided filtered air moving horizontally at 85 feet per minute with 545 air changes per hour and filtration of 99.9 percent of particles as small as 0.5 microns in diameter. A clean area was established by sliding safety glass panels, and two instrument pass-through doors were built into these panels. In all cases monitored, the instrument table was placed adjacent to one of the pass-through doors and one of the pass-through doors was used to deliver sterile packs or trays of instruments to the instrument table.

TABLE 5a.—(Study I) *Total species of organisms recovered from slit sampler during 50 total hip operations done in a laminar flow room with conventional masks*

Case No.	*Minutes*	*Bacteria/ Cubic Foot/ Minute*	*Organisms Recovered from Slit Counter*
1	110	0.395	41 B. subtilis; 1 Alcaligenes
2	110	0.4	5 B. subtilis; 42 Staph. Coag. Neg.
3	75	0.04	1 Colony enterobacter group
4	95	0.09	4 Staph. Coag. Neg.; 3 B. subtilis; 1 Gaffkya tetragena
5	165	0.06	5 B. subtilis; 2 Staph. Coag. Neg
6	100	0.02	1 Herellea; 1 B. subtilis
7	105	1.7	153 B. subtilis; 17 Staph. Coag. Neg.; 10 Staph. Coag. Positive
8	115	0.13	23 B. subtilis; 3 Staph. non-hem. Coag. Neg.; 4 non-hem. Coag. Positive
9	95	0.04	2 Staph. Coag. Neg.
10	105	0.95	85 B. subtilis; 3 Achromobacter; 1 Staph. Coag. Neg.; 6 sarcina lutea
11	110	0.06	2 B. subtilis; 2 Staph. non-hem. Coag. Neg.
12	30	0.03	1 Gram-rod Neg. (failed to grow out on sub-culture)
13	170	0.064	5 Staph. Albus non-hem. Coag. Neg.; 1 Poly-morpha; 1 B. subtilis
14	110	0.065	3 B. subtilis; 1 sarcina lutea; 1 Klebsiella-E uterobacter
15	105	0	0
16	110	0.09	5 sarcina lutea; 2 Gaffkya tetragena; 3 Staph. Coag. Neg.
17	130	0.1	8 Staph. epidermidis; 1 B. subtilis
18	110	0.2	1 Gaffkya tetragena; 4 Staph. epidermidis; 15 B. subtilis
19	130	0.03	3 Staph. epidermidis
20	65	0.1	1 Gaffkya tetragena; 5 Staph. epidermidis; 1 B. subtilis
21	110	0.081	1 Staph. epidermidis
22	110	0.23	17 sarcina lutea; 4 Staph. epidermidis; 5 B. subtilis
23	135	0.21	3 sarcina lutea; 6 Staph. epidermidis; 1 B. subtilis
24	50	0.16	5 Staph. epidermidis; 1 yeast; 2 Diphtheroids
25	110	0.03	1 Staph. epidermidis; 2 B. subtilis
26	110	0.04	2 Staph. epidermidis
27	110	0.2	1 Staph. epidermidis
28	95	0.03	2 Staph. epidermidis
29	135	0.17	7 Staph. epidermidis; 4 B. subtilis
30	140	0.04	2 B. subtilis
31	85	0.033	1 Staph. Aureus
32	105	0.03	2 sarcina lutea
33	115	0.06	1 B. subtilis; 1 Staph. non-hem.; 5 Neisseria catarrhalis
34	110	1.53	155 Staph. epidermidis; 10 sarcina lutea; 3 B. subtilis
35	110	0.04	3 Staph. epidermidis; 1 sarcina lutea
36	130	0.17	1 Gram Neg. rod unidentified; 6 B. subtilis; 2 Staph. epidermidis
37	125	0.493	100 N. catarrhalis; 1 Staph. epidermidis; 1 Staph. citreus
38	110	0.11	6 Gaffkya tetragena; 6 Staph. epidermidis
39	105	0.13	13 Staph. epidermidis; 1 B. subtilis
40	100	0.03	1 B. subtilis; 1 Gaffkya tetragena; 1 Staph. epidermidis
41	145	0.05	11 Diphtheroids and Staph. epidermidis
42	105	0.09	4 Staph. epidermidis; 2 B. subtilis; 1 Strep. non-hem.; 2 N. catarrhalis
43	90	0.01	1 sarcina lutea
44	115	0.05	1 B. subtilis; 1 Staph. epidermidis
45	90	0.2	19 Gaffkya tetragena; 1 Staph. epidermidis
46	110	0.04	2 Diphtheroid; 1 B. subtilis; 1 Staph. epidermidis
47	115	0.08	4 B. subtilis; 5 Diphtheroids
48	165	0.12	9 B. subtilis; 5 Staph. epidermidis
49	115	0.08	9 Gaffkya tetragena and Staph. epidermidis
50	105	0.02	1 Diphtheroid

B. subtilis = Bacillus subtilis
Staph. Coag. Neg. = Staphylococcus Coagulase Negative
Staph. non-hem. Coag. Neg. = Staphylococcus non-hemolytic Coagulase Negative
N. catarrhalis = Neisseria catarrhalis

In order to make all subsequent data more meaningful, every effort was made to eliminate variations in the cleaning and operation of this, our "control" operating suite.

Group II—This group consisted of 50 patients in whom total hip replacement was carried out in a horizontal laminar flow room. All patients were prepared, draped and positioned identically. Pro-

TABLE 5b.—(Study I) *Total species of organisms isolated on settling plates during 50 total hip operations done in a laminar flow room with conventional masks*

Case No.	Minutes	Total Bacteria-Settling Plates	Organisms Recovered from: Instrument Table		Tape Dispenser		Back Table
1	110	3	1 B. subtilis	0		2	B. subtilis
2	110	2	0	1	Staph. Coag. Neg.	1	Staph. Coag. Neg.
3	75	0	0	0		0	
4	95	8	0	0		8	Staph. Coag. Neg.
5	165	9	2 B. subtilis	1	Alcaligenes	5	Staph. Coag. Neg.; 1 sarcina sp.
6	100	1	1 Staph. Coag. Neg.		None	1	Staph. Coag. Neg.
7	105	3	1 Staph. Coag. Neg.	0		1	B. subtilis; 1 Staph. Coag. Neg.
8	115	0	0	0		0	
9	95	1	0	0		1	Staph. Coag. Neg.
10	105	10	0	1	Staph. Coag. Neg.	3	B. subtilis; 6 Staph. Coag. Neg.
11	110	6	3 Staph. Aureus Coag. Positive	3	Staph. Albus Coag. Neg.	0	
12	30	2	1 Staph. Albus Non-hem. Coag. Neg.		None	1	Staph. Albus non-hem. Coag. Neg.
13	170	1	0	0		1	Staph. Albus non-hem. Coag. Neg.
14	110	0	0	0		0	
15	105	2	0	0		2	Gaffkya tetragena
16	110	2	0	0		1	B. subtilis; 1 Staph. Coag. Neg.
17	130	0	0	0		0	
18	110	3	0	0		3	Staph. epidermidis
19	130	6	1 Staph. epidermidis	3	Staph. epidermidis	2	Staph. epidermidis
20	65	3	0	0		3	Staph. epidermidis
21	110	0	0	0		0	
22	110	6	0	2	Staph. epidermidis	4	Staph. epidermidis
23	135	6	0	2	Staph. epidermidis	4	Staph. epidermidis
24	50	1	1 Staph. epidermidis	0		0	
25	110	3	0	1	Staph. epidermidis	2	Staph. epidermidis
26	110	19	0	1	Diphtheroid	18	Staph. epidermidis
27	110	2	0	0		2	Staph. epidermidis
28	95	2	0	2	Staph. epidermidis	0	
29	135	0	0	0		0	
30	140	3	0	2	Staph. epidermidis	2	Staph. epidermidis
31	85	1	0	0		1	B. subtilis
32	105	0	0	0		0	
33	115	2	1 B. subtilis	1	B. subtilis	0	
34	110	14	0	2	Staph. epidermidis	1	B. subtilis; 11 Staph. epidermidis
35	110	19	0	5	Staph. epidermidis	14	Staph. epidermidis
36	130	1	0	1	Staph. epidermidis	0	
37	125	8	1 N. catarrhalis; 1 sarcina lutea; 3 Staph.	0		1	B. subtilis; 2 Staph. epidermidis
38	110	4	1 Staph. epidermidis	1	Staph. epidermidis	2	Gaffkya tetragena
39	105	0	0	0		0	
40	100	3	1 Staph. epidermidis	1	Staph. epidermidis	1	Staph. epidermidis
41	145	13	0		None	13	Diphtheroids
42	105	0	0	0		0	
43	90	0	0	0		0	
44	115	1	0	0		1	B. subtilis
45	90	7	0	0		2	Staph. epidermidis; 5 Gaffkya tetragena
46	110	0	0	0		0	
47	115	3	0	3	Staph. epidermidis	0	
48	165	2	0	0		1	Staph. epidermidis; 1 Achromobacter
49	115	4	0	0		4	Diphtheroid, Gaffkya tetragena, Staph. epidermidis
50	105	0	0	0		0	

See Table 5a for abbreviations

phylactic antibiotics were used in all cases, and all members of the operating team wore two standard paper masks and were gowned and gloved in an identical manner. Routine irrigation of the wounds was done with a triple antibiotic solution (neomycin, polymyxin B and bacitracin). All members of the operating team were positioned to minimize interference with the laminar air flow. Operative site as well as settling plate monitoring was done on all 50 patients. The procedures were carried out by 19 different surgeons.

Group III—The Group III patients included 27 patients undergoing total hip replacement prepared in an identical fashion to the Group II cases. However, in this group the operative team utilized a suction-mask aspiration system. The vacuum pump was connected to a manifold with four intakes in the base of the laminar flow filter bank. Air was evacuated from each head set at the rate of five cubic feet per minute. The 27 operations monitored were done by 13 different orthopedic surgeons.

Group IV—Five patients undergoing total knee replacement were monitored in the laminar flow room using suction hoods in an attempt to determine the effect on bacteria at the operative site during procedures that increase interference with laminar air flow by the surgical team. Both operative site and settling plate monitoring was done.

Group V—In the Group V cases, seven surgical procedures, not involving the hip joint, were monitored. The operating team in this group used conventional masks and gowns.

Group VI—In the Group VI, or "control" group, ten one-hour periods were monitored in the laminar flow room with the room empty.

STUDY II

In this study, bacteria were monitored using only the slit sampler during simulated operative procedures.

Group A—This group was done to determine if the operated leg shed significant numbers of bacteria when draped in a conventional manner for total hip replacement. Monitoring was done for one hour; and during this sampling, the simulated patient moved her "operated" hip through a full frog-leg position once every five minutes. No other persons were allowed in the operative suite.

Group B—A standard operating room table was draped in the usual fashion and elevated to the average height off the floor as during total hip replacement. The Casella counter was utilized in the standard fashion. The team of three wore conventional nonsterile head gear and one mask then gowned and gloved in the usual fashion. Bacterial monitoring was done as they carried out a simulated total hip replacement procedure. This team then simulated the usual motions of an operating team during a hip replacement, except that the pass-through doors were not opened and the movable light fixtures were not handled. Six separate "operations" were monitored in this manner.

Group C—Six simulated procedures were monitored with the operating team using a suction-mask aspiration system. Again, the operating team moved about the room without handling the light fixtures or the pass-through doors.

Group D—In the Group D cases, the simulated operative team wearing conventional masks moved about the laminar flow room as if doing a total hip replacement while operation site monitoring was done. In this Group D study, the operating team also moved the light fixtures and the pass-through doors approximately the same number of times as during usual total hip procedures.

Group E—In six cases, the simulated operating team wore suction-mask system equipment while they carried out a simulated total hip replacement procedure. As in the Group D study, the team moved the light fixtures and the pass-through doors as during total hip replacement.

Group F—In this "control" group, four simulated hip studies were done with the operating team wearing clean, but not sterile, operating room attire and no gloves. Two simulated operations were done with team members wearing one paper mask each and two with no masks. In all four cases, the skin of the operating team's upper extremities was exposed from the mid-arm distally.

In all groups, talking was limited to the amount and volume usually done during hip surgical procedures.

Results

STUDY I

Groups I, II and III—Table 1 summarizes the results in Groups I, II and III, Study I. As it indicates, the number of bacteria per cubic foot per minute dropped from 3.74 in a conventional operating room to 0.18 in a laminar flow with

conventional masks. Then in a horizontal laminar flow with suction masks, there is a further drop to 0.05. These results are statistically significant at the .001 and .05 levels respectively using the T-test.

Therefore, there was a 95 percent reduction in bacteria isolated at the wound site in the operations monitored in the horizontal laminar flow as compared with operations monitored in a conventional operating room. A further 72 percent reduction in mean bacteria per cubic foot per minute occurred in hip surgical operations done in a laminar flow room with the addition of a suction-aspiration unit when compared with hip operations done in a laminar flow room with conventional masks and gowning. Table 2 summarizes these data. Operations done in a laminar flow system with a suction-hood aspiration system had a 99 percent reduction in numbers of bacteria when compared with a conventional operating room.

Group IV—In total knee replacements during which suction masks were used, the mean bacteria per cubic foot per minute was .04 in five cases (Table 3).

Group V—In Group V, in which operations other than total hips were done, the mean bacteria per cubic foot per minute was 0.45 (Table 3).

Group VI—In Group VI, the control group, no bacteria were cultured in ten one-hour periods in the empty laminar flow room.

STUDY II

Group A—In the simulated patient study, no bacteria were recovered in any of the seven one-hour monitoring periods.

Group B—Six cases were monitored for one hour each with the operating team using conventional head gear in the horizontal laminar flow room. Two colonies of Bacillus subtilis were isolated (.005 bacteria per cubic foot per minute).

Group C—Six cases were monitored for one hour in an identical fashion to the Group B cases except that the operating team used a suction-hood mask aspiration system. No bacteria were isolated in this group.

Group D—Six simulated operations were monitored for one hour with the operating team in conventional gowns and masks in the laminar flow room and with the operating team moving

TABLE 6a.—(Study I) *Total species of organisms isolated on settling plates during 27 total hip surgeries done in a laminar flow room with a suction-hood system*

Case No.	*Minutes*	*Bacteria/ Cubic Foot/ Minute*	*Organisms Recovered from Slit Counter*
1	120	.08	10 B. subtilis, Staph. epidermidis and sarcina lutea
2	55	.08	1 B. subtilis; 7 Gaffkya tetragena; 4 Staph. epidermidis
3	90	.22	1 B. subtilis; 1 Staph. epidermidis
4	137	.01	1 Staph epidermidis; 1 B. subtilis
5	78	.05	1 Staph epidermidis; 1 Gaffkya tetragena; 2 B. subtilis
6	100	.02	2 Staph epidermidis
7	105	.038	1 Aspergillus; 3 B. subtilis
8	85	.01	1 Staph. epidermidis
9	106	.01	1 B. subtilis
10	95	.03	1 Achromobacter; 2 Staph. epidermidis
11	100	.06	5 Staph. epidermidis; 1 B. subtilis
12	90	.02	1 Staph. epidermidis; 1 Torulopsis sp.
13	85	.023	1 B. subtilis; 1 Staph. epidermidis
14	115	.02	1 Diphtheroid; 1 Staph. epidermidis
15	85	.02	2 Staph. epidermidis
16	195	.07	11 sarcina lutea; 1 Staph. epidermidis
17	120	.075	4 B. subtilis; 6 sarcina sp.
18	135	.02	2 Staph. epidermidis
19	55	.18	1 Bacillus publilis
20	110	.13	14 sarcina lutea
21	73	.05	3 Staph. epidermidis; 1 B. subtilis
22	115	0	0
23	110	.9	2 sarcina lutea; 5 Staph. epidermidis; 3 B. subtilis
24	105	.03	2 B. subtilis; 1 Staph. epidermidis
25	31	.06	1 Staph. epidermidis; 1 Diphtheroid
26	115	.03	4 Staph. epidermidis
27	120	.14	13 sarcina lutea; 3 Staph. epidermidis

See Table 5a for abbreviations

the lights and pass-through doors. One colony of Bacillus subtilis was cultured.

Group E—Six cases were monitored for one hour in an identical fashion to the Group D cases except that the operating team used a suction-mask system. No bacteria were cultured in this group.

Group F—Four cases were monitored in the horizontal laminar flow room with clean, but non-sterile apparel worn by the operating team. In two cases, no masks were worn and nine colonies of Staphylococcus epidermidis, two colonies of Bacillus subtilis and one colony of an Alpha streptococcus were isolated. In the cases monitored with the operating team members each wearing a single mask, seven colonies of Staphylococcus epidermidis were isolated.

Table 7 summaries the data from all of the groups in Study II.

Discussion

In cases monitored both at the operative site using a slit sampler and with settling plates, there is poor correlation in the species of bacteria isolated.

Numerous discrepancies were noted. There was an 80 percent discrepancy in the species of bacteria isolated at the instrument table settling plate versus the operative site in the Group II cases and a 100 percent discrepancy in the Group III cases. Comparison of Table 5a and Table 5b shows these discrepancies for Study I.

There are several possible explanations for these differences. Most likely, the operating team is the greatest single source of airborne bacterial contamination because they are clustered near the operative site and therefore are affecting airborne bacteria at the operative site and at settling plates differently. Other factors that may be important are (1) effects on instrument table settling plates by airborne bacterial contamination through pass-through doors and (2) differences in culturing methods between a split sampler and settling plates.

Of particular importance, note the significantly greater numbers of bacteria cultured from the operative site in Groups II and III as compared with the settling plate at the instrument table (Tables 5a and b and Tables 6a and b).

There were two early deep wound infections

TABLE 6b.—(Study I) *Total species of organisms isolated on settling plates during 27 total hip operations done in a laminar flow room with a suction-hood respiration system*

Case No.	Minutes	Total Bacteria-Settling Plates	Organisms Recovered from: Instrument Table	Tape Dispenser	Back Table
1	120	15	0	8 Staph. epidermidis and sarcina lutea	2 Pseudomonas maltophilia; 8 Staph. epidermidis and sarcina lutea
2	55	5	1 sarcina lutea	0	1 Diphtheroid; 3 Staph. epidermidis
3	90	3	0	0	3 Staph. epidermidis
4	137	9	1 B. subtilis	2 Staph. epidermidis	5 Diphtheroids; 1 Staph. epidermidis
5	78	0	0	0	0
6	100	1	0	0	1 Staph. epidermidis
7	105	0	0	0	0
8	85	3	0	1 Staph. epidermidis	2 Staph. epidermidis
9	106	4	0	1 Staph. epidermidis	1 B. subtilis; 1 Diphtheroid; 1 Staph. epidermidis
10	95	5	0	2 Staph. epidermidis	2 Staph. epidermidis; 1 B. subtilis
11	100	20	1 Staph. epidermidis	0	18 Staph epidermidis; 1 B. subtilis
12	90	0	0	0	0
13	85	4	0	1 Achromobacter	2 Alcaligenes; 1 Staph. epidermidis
14	115	2	0	0	2 Staph. epidermidis
15	85	3	0	1 Staph. epidermidis	2 Staph. epidermidis
16	195	2	0	1 Staph. epidermidis	1 Staph. epidermidis
17	120	1	0	0	1 Staph. epidermidis
18	135	9	0	0	7 Staph. epidermidis; 2 Mima polymorpha
19	55	1	0	0	1 Staph. epidermidis
20	110	2	0	2 Staph. epidermidis	0
21	73	2	0	1 sarcina lutea	1 Diphtheroid
22	115	3	0	0	3 Staph. epidermidis
23	110	none	none	none	none
24	105	5	0	0	4 sarcina lutea; 1 Staph. epidermidis
25	31	0	0	0	0
26	115	2	0	1 Staph. epidermidis	1 Staph. epidermidis
27	120	0	0	0	0

See Table 5a for abbreviations

and no superficial wound infections in these series of patients. In both wound infections, settling plate monitoring only was done. Both of the two early deep wound infections occurred in cases monitored with settling plates only in the laminar flow room with conventional masks and gowns. No early or late superficial or deep wound infections occurred in either the Group II or Group III cases.

In one patient a total knee replacement became infected with Pseudomonas aeruginosa with drainage beginning two weeks after operation. Settling plate studies done at the time of operation yielded only Staphylococcus epidermidis with no Pseudomonas aeruginosa isolated. The infection in this case was a continuing serious deep infection that necessitated removal of all the prosthetic components. Within four months after removal of these components, spontaneous fusion of the knee occurred and there has been no further drainage.

The second early deep wound infection occurred in a patient in whom a total hip replacement was done and cultured Staphylococcus aureus coagulase positive ten days after operation. The infection did not respond to systemic antibiotics, and it was deemed essential to remove the prosthetic components. During induction of anesthesia for this surgical procedure, cardiac arrest occurred and the patient died before the procedure was begun, in spite of extensive resuscitative measures.

In the case of the deep wound infection of the knee, four colonies of Staphylococcus epidermidis were cultured in the settling plate near the hall door. No colonies were isolated in the tape dispenser settling plate, and two colonies of Staphylococcus epidermidis were isolated at the settling plate on the instrument table.

In the deep wound infection of the hip, the instrument table settling plate grew out one Staphylococcus epidermidis and the tape dispenser settling plate grew out two colonies of Staphylococcus epidermidis.

Table 4 summarizes the bacteria isolated at the operative site during monitoring of the Group II and Group III, Study I, cases. Some similarities such as the large and similar numbers of Staphylococcus epidermidis and the low numbers of Staphylococcus aureus are noted. The major differences appear to be in the high percentage of Sarcina noted in the Group III, Study I, cases and the lower Bacillus subtilis percentage in the Group III, Study I, cases. In absolute numbers of bacteria isolated, these differences are not so striking.

Sources of Experimental Error

There are many sources of experimental error in studying airborne bacteria in the operating suite. It is likely that only a small number of the bacteria that actually appear at the operative site are recovered with the slit sampler. Furthermore, certain species of bacteria may be harder to culture than others; and this may lead to distortion of the relative numbers and types of bacteria recovered at the operative site.

When this study was begun in 1971, closing cultures were not routinely done. These cultures would have made the interpretation of airborne contamination at the operative site more significant. Nelson, Glassburn and their co-workers[17] have shown a reduction in positive cultures with the addition of a laminar flow system and a laminar flow system plus suction-hoods. Others have shown that the slit sampler which was used in this study may be less efficient in monitoring bacteria than a gelatin membrane sampler.[18]

Anaerobic cultures were not done, and it is possible pathogenic anaerobic organisms were present at the operative site. The temperature of the operating room varied between 68 and 74°F dur-

TABLE 7.—(Study II) *Comparison of numbers of bacteria isolated during simulated surgical procedures*

Group	*No. of Cases*	*Key Variable*	*Mean Bacteria/ Cubic Ft./ Minute*
A	7	No O.R. team	0
B	6	No patient; conventional mask	.005
C	6	No patient; suction mask	0
D	6	Conventional mask; light and doors moved	.003
E	6	Suction mask and lights moved	0
F	4	No patient; operating team in nonsterile apparel	.075

O.R. = Operating room

ing data collection, and this factor was not considered.

In the Group II, Study I, cases, 19 different surgeons were involved. Study of each surgeon's data separate from the rest of the data and separate from each other did not show any significant difference in types or species of bacteria.

In comparing the numbers of bacteria isolated in Study I versus Study II, a pronounced difference is noted. This difference could be due to the short time of monitoring (one hour), temperature differences in the room or differences in shedding by operating team personnel when they are actually carrying out surgical operations as opposed to simulated procedures.

Conclusions

- Until the exact importance of airborne contamination of wounds in causing clinical wound infections is better established, laminar flow systems and suction-hood systems must be considered experimental.
- Horizontal laminar flow with conventional head gear reduced bacterial airborne contamination at the wound site by 95 percent over counts in a conventional operating room. Addition of a suction-hood system reduced bacterial counts an additional 72 percent.
- Operative site bacterial counts in total knee replacements done in a horizontal laminar flow system with a sterile suction mask system are comparable to total hip replacements. However, routine orthopedic procedures that involve obstruction of the laminar flow by the operative team wearing conventional masks and gowns resulted in operative site bacterial counts considerably higher than during total hip replacements where there was less interference with the laminar flow.
- The well-draped patient did not appear to be an important source of airborne contamination at the operative site during one hour of monitoring in a horizontal laminar flow system during simulated surgical operation.
- Fomitic sources of bacteria in the horizontal laminar flow room such as light fixtures, passthrough doors, movement of properly attired personnel between the operative field and the high efficiency particulate air (HEPA) filter bank and the ensuing motion of floor bacteria did not appear to be sources of airborne bacteria in a horizontal laminar flow system in one hour of monitoring during simulated surgical procedures.
- Any study of airborne contamination of an operative suite must include both operative site and settling plate studies since there is poor correlation between the species of bacteria isolated at the operative site and those recovered with settling plates.
- Operative site monitoring will recover more organisms and is probably of greater significance in assessing airborne contamination of the operative wound. However, settling plate studies of the instrument table may be important in assessing instrument contamination which, in turn, could be important in direct contact contamination of operative wounds.

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A System for Evaluating and Treating Chronic Back Disability

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Five methods of personality assessment are evaluated to provide guidance for the psychological treatment of patients with chronic back pain. Patient pain drawings, pentothal pain studies, stress score index, psychological testing with the Minnesota Multiphasic Personality Inventory (MMPI) and response to treatment challenge are used as measurements for evaluation. This evaluation gives the treating staff guidelines for individual treatment programs utilizing operant conditioning techniques. Using this approach, three fourths of the severely disabled patients seen have been successfully treated.

THE PURPOSE of this paper is to describe a method to evaluate cases of patients with prolonged pain disability. This evaluation has been developed in order to provide guidelines for establishing an active treatment program for such patients.

The patients with prolonged pain disability whom we have studied have had chronic back and neck complaints associated with variable referred pain patterns into the limbs. Our experience in the study and treatment of these patients has been developed from the program at the Problem Back Treatment Center, Rancho Los Amigos Hospital. This program has been functioning for more than four years and in this time more than 700 inpatients with chronic benign pain complaints have been treated. Three quarters of these patients have had previous back and neck surgical operations, averaging nearly 2½ operations per patient. They generally have had prolonged disability, with the average time away from work approaching 2.2 years. The discussion in this paper deals primarily with the psychological evaluation in these cases of severely and chronically disabled patients.

Background

The measurement of pain and human reaction to pain remains one of the most frustrating aspects of clinical medicine. Especially for a surgeon, with his need to feel or see before he can rationally operate, the identification of a specific structural site accounting for a patient's complaint of pain is a necessary goal. But in the case of chronic back disease, without specific neurologic localiz-

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ABBREVIATIONS USED IN TEXT

MMPI = Minnesota Multiphasic Personality Inventory
TPR = topographical pain representation

ing signs, a clinician is often left with only symptoms which are described by a patient in a number of different ways, depending on many subtle human factors—but with no significant physical signs or laboratory findings.

The variability of human reaction to apparently similar structural sources of pain is best shown in the findings of Wiltse's recent study.[1] In this prospective double-blind study of a significant series of patients suffering from surgically treatable lumbar disc disease, 90 percent did very well after treatment if their psychological testing showed no tendency toward hypochondriasis or symptoms of conversion reaction. On the other hand, only 10 percent of patients with essentially similar signs and symptoms did well if their psychometrics showed them to be severely hypochondriacal or conversional. Moreover, in this study physicians were not shown to be particularly adept at evaluating personality factors as predictors before surgical operation.

One of the most effective concepts for the understanding of variable human reaction to pain is the idea of psychogenic magnification of pain as suggested by Alan Walters of Toronto.[2] The concepts of psychogenic regional pain and psychogenic magnification of pain are simplistic but nonetheless useful frameworks for the understanding of human reaction to pain. The concept avoids mystifying psychodynamics to explain pain symptoms that exceed purely anatomic bases.

Recently there has been an emerging understanding by surgeons treating patients with chronic back disabilities that some pain cannot be cut away by surgical operation, no matter how frequently it is tried.[3] Moreover, it has been recognized that it is possible for a "career of pain" to develop as a person's primary method of human interrelationship.[4] The tendency for a "painful person" to use this maneuver as his method of coping is now well understood in the psychological literature[5] and is beginning to have an impact in clinical medicine. Various programs have been started which not only take into consideration the interweaving of reaction to pain with structural source but also include active treatment programs focused on pain behavior rather than pain sources.[6]

The program at Rancho Los Amigos Hospital initially was modeled after a program in Seattle organized by Fordyce.[7] As our own experience increased, the treatment and evaluation systems have been varied considerably from those of the model program to respond to our own needs and skills.

In our program, every effort is made to discover the structural sources of pain by conventional diagnostic procedures. In addition, a combination diagnostic-therapeutic approach is used to unravel the structural sources of pain. When indicated to be appropriate by clinical findings, injection of local anesthetic and an anti-inflammatory agent (steroid) is carried out in the facet joints, spinal canal and intervertebral disc with the aid of fluoroscopic control. Based on patient response to injection, diagnostic information is obtained. Frequently, persistent relief of complaints is possible from these injections. We feel this is a rational approach to dealing with anatomic pain sources that do not present true signs of neurologic deficit. Occasionally surgical procedures are carried out when anatomic sources are significant and pain is not completely relieved by injection.

We recognize, however, that in the case of chronic pain disability, reaction to persistent chronic pain may build upon these primary sources and provide additional and significant sources for complaints. In order to estimate the degree of pain magnification, a systematic attempt is made to document and quantify psychogenic reaction to persistent pain. Then, based on a knowledge of the interrelationship between structural sources of pain and psychogenic pain reactions, a rational treatment program can be started —when one is appropriate—that is focused on treatment of painful behavior as well as painful sources.

Workup

The first requirement for a systematic workup is that the data regarding the historic events in the pain complaint be drawn from a standardized form. Therefore, before entering the program all persons fill out a patient history form (Figure 1). In a question-and-answer section of the form, all the pertinent historic details are summarized. The duration of the disability, the current extent of the problem, and the temporal and postural orientation of the pain are noted. Finally, information

Name _____ RLAH # _____

Age _____

Rancho Los Amigos Hospital
Problem Back Treatment Center
COUNTY OF LOS ANGELES • DEPARTMENT OF HEALTH SERVICES

PATIENT HISTORY FORM

1. How long have you had the present pain? _____ weeks _____ months _____ years
2. How long have you had any trouble with your back, legs, or neck? _____
3. How long have you been off work or unable to do normal housework? _____
4. Did your pain begin: ____ gradually ____ suddenly ____ from an injury
   ____ while lifting ____ while twisting ____ at work
5. My pain is: (check appropriate box)

	Better	Worse	Unchanged
a. when I awake in the morning	☐	☐	☐
b. bending forward to brush teeth	☐	☐	☐
c. with cough or sneeze	☐	☐	☐
d. sitting down at a table	☐	☐	☐
e. sitting in an automobile	☐	☐	☐
f. during the middle of the day	☐	☐	☐
g. just before bed time	☐	☐	☐
h. during the middle of the night	☐	☐	☐
i. lying on my back	☐	☐	☐
j. lying on my stomach	☐	☐	☐
k. lying on my side with knees bent	☐	☐	☐

6. What is the most aggravating thing about your pain? _____ _____
   _____
7. How many times have you been in a hospital for back, leg, or neck problems? _____
8. Have you had Myelograms? ___ yes ___ no # ___ EMG's? ___ yes ___ no # ____
9. Have you had previous back surgeries? ___ yes ___ no # ___ type? _____
   _____ when? _____
10. Have you had other types of surgeries? ___ yes ___ no # ___ type? _____
    _____ when? _____
11. Have any treatments ever made the pain better? ___ yes ___ no what treatments? ____
    _____
12. Have any treatments ever made the pain worse? ___ yes ___ no what treatments? ____
    _____

Figure 1.—Patient history form, providing a standardized data base for significant historical points.

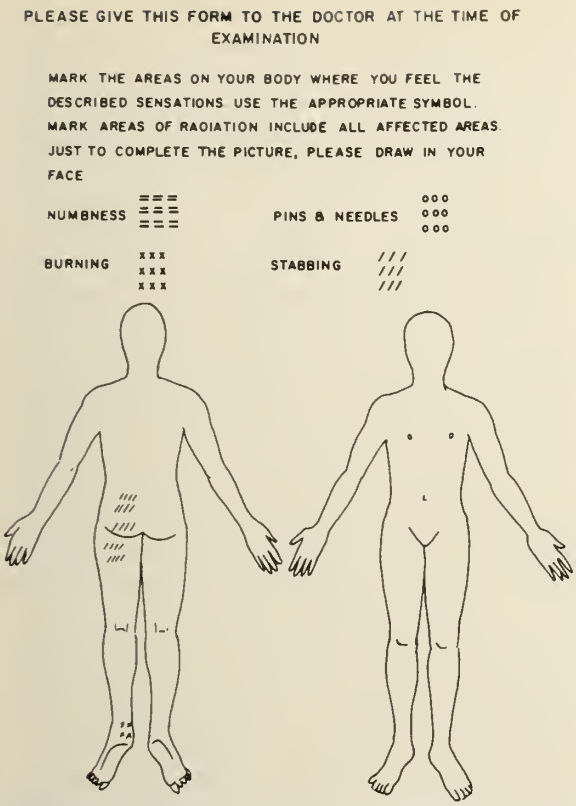

Figure 2.—A topographical pain representation of a 35-year-old man with all the signs and symptoms consistent with a diagnosis of protruding lumbar disc. The diagnosis was confirmed by myelography and discography. Patient's pain complaints were considered anatomically justified.

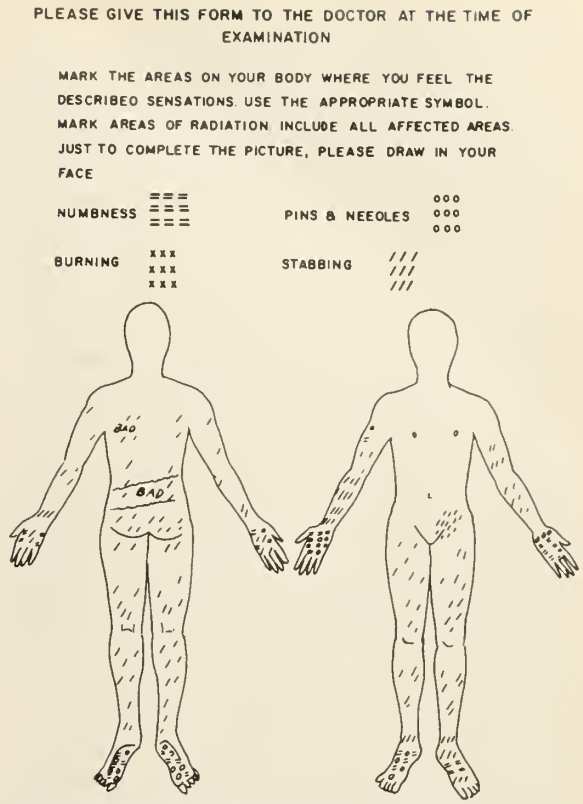

Figure 3.—A topographical pain representation of a 35-year-old-woman who has already had two lumbar operations but continues to have complaint of pain in many locations. Psychological testing suggests considerable magnification of pain and pentothal examination is nonperipheral.

about past treatment programs is filled in. Knowing the number of previous surgical operations and admissions to hospital is essential when evaluating habituation to disability. And knowing which treatment programs have helped in the past, and which have not, will give some guidance as to future treatment.

Use of this form has also been found to save considerable amount of time in the general orthopedic office. Although most patients seen in private orthopedic practice do not have the persistence and severity of chronic pain complaints that patients in the Problem Back Clinic have, nonetheless summaries of their complaints in a systematic format makes it possible for a clinician to more rapidly assimilate the pertinent historic events.

In the workup in our clinic a vigorous effort is made to provide quantitative and qualitative data on the pain behavior of the patient. The elements of this data base take the form of patient pain drawings, pentothal pain study, life change stress index, psychological testing using a Minnesota Multiphasic Personality Inventory (MMPI) and response to treatment challenge. Each of these will be described in some detail.

Patient Pain Drawings

The use of patient pain drawings was developed as a method to improve communication between patients and clinicians. Frequently, spoken description of pain by a patient is not sufficiently explicit because of educational, language and experience differences between patients and physicians—who obviously are more anatomically oriented. Moreover, comparing pain in one patient with that in another is extremely difficult using spoken descriptions by patients. Therefore, in an attempt to discover potential neurologic deficits, we asked patients to indicate the location of pain on a human form outline and to characterize the pain with symbols as much as possible. These topographical pain representations (TPR's) have been very useful in summariz-

ing patients' descriptions of the nature and location of pain.

As experience with TPR's increased, it was found—to our surprise—that these representations could be seen as graphic displays of psychogenic regional pain and psychogenic magnification of pain phenomena. Patients in whom there was crisp and precise localization of pain clinically were those who tended to have significant discogenic disease, frequently of recent and acute onset or with classical signs and symptoms. Those whose TPR's showed expanded areas of pain localization, frequently with florid descriptions of intensities of pain, tended to be those with a history of chronicity and multiple surgical operations, and in whom traditional medical treatment approaches had not been completely successful (Figures 2 and 3). Using pain drawings alone it is possible to pick with a 75-percent accuracy those patients in whom eventual workup identifies significant emotional involvement in their disease.[8]

Topographical pain representations have now become the most significant single source of data in evaluating the type of problem we deal with. They act as a permanent record of a patient's pain complaints, as well as providing significant data about a patient's response to anatomic disease.

Not only is it difficult to evaluate a patient's verbal description of pain, but physical limitations caused by a patient's pain frequently are subjective and equally difficult to evaluate. Such physical signs as deficiency in straight leg raising, sites of acute tenderness, areas of diminished sensation and protective muscle spasm are all common complaints of both patients with acute onset of disability and those whose back or neck difficulties have lasted for years. It is frequently difficult to assess to what extent these complaints are due to anatomic-neurologic factors and to what extent they result from habituation or expectation of pain.

Pentothal Pain Study

A method of evaluation first advocated by Walters and expanded by McNab has worked very well in assessing pain complaints.[9] This method, the pentothal pain study, utilizes short-acting barbiturates to create a hypnotic state in which the patient is oblivious to all acute pain sources of moderate severity such as squeeze of the Achilles tendon or pin prick. Next, the patient is allowed to recover from this level of somnolence to a state in which he will respond by limb withdrawal to these painful stimuli. At that moment the physical sign in question (straight leg raising deficiency, acute tenderness sites, and so forth) is challenged to the patient. If his response is similar to that noted on physical examination when he was awake, the pain source is identified as being peripheral. If at this level of light anesthesia the patient apparently is oblivious to what was an obvious source of pain when he was awake, the pain source is identified as nonperipheral. Whenever possible the physical examiner who noted the pain response with the patient awake should be the same one who carries out this physical test with the patient under light anesthesia. Of course, the normal precautions of general anesthesia are taken and in our facility this test is done by a nurse anesthetist with routine resuscitative equipment at hand.

It is important to recognize that the implications of this test are not that a patient has been simulating physical signs or malingering. In most of our patients, future workup indicates that a nonperipheral response on physical testing is made completely on an unconscious level and the patient has not been consciously dishonest with himself or the clinician. The test is very useful, however, in distinguishing pain due to disease processes and having significant structural basis from that in which the structural sources are minimal and the pain noted by the patient is a reaction or a magnification of insignificant anatomic abnormalities. Those patients in whom pain has significant structural basis receive appropriate anatomic treatment such as surgical operation or steroid injection.

Life Change Stress Index

Another method for evaluating a patient's reaction to disability is the Life Change Index, developed by Holmes and Rahe in 1967.[10] It consists of a list of 43 events relating to personal, social and economic situations. Patients are asked to check off any of the events that have occurred in their lives within the past two years. Each event is considered to be a source of stress and weighted with a certain number of points. Events range from the relatively minor event of receiving a traffic ticket (11 points) to the death of a spouse (100 points). The points are totaled and stress score results. Holmes and Masuda (1972)[11] report low stress scores to be 150 to 199, medium

stress scores to be 200 to 299 and high stress scores to be 300 points or more. A survey of 75 patients admitted recently to our program found a mean life change index score of 283, with a range from 91 to 607 points. These scores not only represent stress levels but also the degree to which a patient's reaction to pain may have resulted in significant events or changes in life style.

Minnesota Multiphasic Personality Inventory

The most common form of objective psychological evaluation is the Minnesota Multiphasic Personality Inventory. The MMPI is composed of 566 affirmative statements to which a patient responds true or false. The responses are plotted as graphs and create a profile representing a patient's personality. Deviations from the norm in ten different areas of personality can be shown by this profile. Although there may be more appropriate systems to evaluate a patient's ability to cope with stress and environment, the extensive use of the MMPI in many areas of personality evaluation has created an extensive background wherein "normal" behavior is fairly well defined. However, deviations from the norm as expressed by responses to the questions in this test must be considered in the context of a patient's entire personality and intellectual and social background. Therefore, although computer readouts of MMPI scores are available, we feel individual weighting of all factors by a psychologist creates a more accurate evaluation of patient response for our purposes.

Having collected nearly 700 MMPI scores from patients having similar pain complaints, we now have a large data base for comparison and rating purposes. Specifically, in addition to showing the general psychological status of a patient, the profiles indicate such factors as the degree to which pain complaints represent a tool in social relationships, whether pain behavior is likely to change and what mechanisms may be applied to accomplish this, and whether a patient has settled comfortably into the role of disability. Our experience emphasizes the point that MMPI results reflect only the state of the patient at the time of taking the test. They do not yield information on causative factors.

In order to develop a rational treatment program, a psychologist must have some knowledge of why a patient exhibits his present behavior. This is accomplished in part through an interview. Here the psychologist determines the contributions of history, family, work and other environmental variables related to the patient's complaints. The MMPI results provide a framework for this critical interview. Consequences of pain complaints are also examined to see if they provide the patient with highly valued attention from others or remove him from some unpleasant situation.

Response to Treatment Challenge

The data source that is most subjective and subject to prejudice is patient response to the challenge of treatment. In developing these data, the observations of the various people able to judge a patient's ability to cope with the stresses of workup and treatment are summarized. These observers include physicians, psychologists and (more important for this data source) those who observe the patient under less threatening conditions. Consequently, nurses and therapists are expected to form opinions as to a patient's method of responding to the stresses of care in hospital. One specific criterion that is available for some quantitation is response to pain medication. In

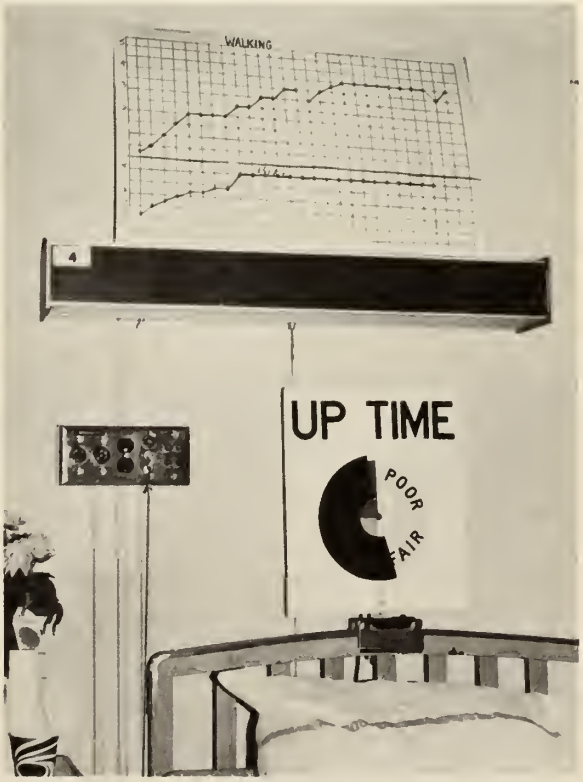

Figure 4.—Graphs above the bed are plotted daily to show a patient's level of functional activity. The "up time recorder" indicates the amount of time spent out of bed and is operated by an electronic monitor connected to the bed.

our program, all medication for pain is given every four hours in 15 ml of cranberry juice with a little quinine added for bitterness. In those patients who previously have been receiving high levels of narcotics, administration of methadone is begun to avoid any rapid withdrawal symptoms. In addition, methadone is used in an effort to avoid the psychotropic effect of other narcotics. When a patient has not been receiving high doses of narcotics for pain, codeine is used as the medication for pain. Based on pain behavior and response to medication, nurses reduce the dosage of methadone or codeine as seems appropriate.

In the pain rehabilitation program, patients are expected to care for their unit independently—make beds and the like. They are expected to participate with other patients in various exercise programs, evaluations and other training activities. Their ability to cope with these challenges is summarized by the staff.

Treatment Program

From the data built up in the various ways described, considerable information is available about a patient's ability to cope with his environment and tendency to magnify his disability, and the balance between structural sources of pain and emotional reaction to it can be understood. This information in itself is useful to medical clinicians because it may verify subjective feelings about a patient's basic personality problems and it may argue against starting vigorous, structurally oriented treatment programs. However, the information alone does not solve a patient's basic problem—persistence of chronic pain. For this, an appropriately oriented clinical psychologist is necessary to carry the treatment program further and to develop a systematic approach to this phase of a patient's disability.

Once the structural treatment program is complete, a clinical psychologist, using data from the various tests and the interview, determines how best to approach poststructural treatment and then starts an appropriate treatment program. Principles of operant conditioning are applied to increase functional activity levels. The focus of poststructural treatment is on improving levels of function. Patients receive praise and attention from staff for functional increases (for example, walking a set distance, using an exercycle, spending an increased amount of time out of bed and discussing subjects other than pain). Various means of making a patient aware of his activity levels are built into the program. Large graphs with levels of activity plotted daily are placed above each patient's bed (Figure 4). Each bed is equipped with an electronic monitor—an "up time recorder"—that shows the amount of time a patient has spent out of bed (Figure 4).

Peer pressure exerts a great influence because the amount of improvement shown by patients is made a competitive matter. In this way, group dynamics are used to evaluate functional levels and reduce habits of disability. Patients attend group sessions to discuss alternative reactions to pain and stress factors, and how to develop social skills not dependent on pain. Family members receive counseling and training in operant techniques to maintain an atmosphere that will support improved function after discharge. Patients who are felt to be good candidates for vocational guidance are given tests to determine interests and abilities, and referred to Vocational Rehabilitation Services.

Evaluation of patient response to follow-up questionnaires indicates that 75 percent of the patients state that treatment resulted in either a significant decrease in pain or increase in activity (average length of follow-up is ten months). Fifty-eight percent stated that they no longer required narcotic pain medications and 74 percent had not felt the need to seek further medical advice.

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Medical
PROGRESS

Prenatal Diagnosis and Genetic Counseling

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Since the early 1960's knowledge regarding human genetics has increased at an exponential rate. Because genetics was not commonly taught in medical schools before the late 1960's, this review article is intended to acquaint physicians or refresh their knowledge regarding chromosomal, mendelian and multifactorial inheritance and the indications for prenatal diagnosis. Establishing an accurate diagnosis and mode of inheritance is essential in identifying and selecting those families at risk for genetic disease in their offspring. Medical genetics is evolving as a specialty in order to provide consultation and, if needed, management of those families who would benefit by genetic services. Families who would benefit from genetic counseling include, for example, those in whom any of the following conditions is present: known chromosomal disorders, known disorders due to mendelian inheritance, mental retardation of unknown origin, failure of sexual maturation or failure of sexual development, congenital malformations, floppy infant syndrome or leukemia.

A list of more than 70 disorders now detectable in a fetus by means of amniocentesis provides a beginning in the prevention of genetic disease. Knowledge regarding these diseases allows a physician to provide families with accurate risk figures so that they may make informed decisions about having children. Also, a compassionate and nonjudgmental approach to counseling is essential. Decisions, in the final analysis, must be made by the family but aided and supported by the physician.

IN THE RECENT PAST, advances in medicine usually have been relatively easy for physicians to understand and accept. The superiority of penicillin to sulfonamides for the treatment of beta streptococcal infections, or the safety of ampicillin compared with chloramphenicol are straightforward medical points. More recently, physicians have been asked to publicly make more difficult choices —for example, who is to undergo renal dialysis or transplants, and how far one should push life-sustaining measures, such as respiratory and cardiac assistance and hyperalimentation. Biology

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has now provided us with information and techniques that will allow us to identify persons whose offspring are at risk for certain genetic disorders. The use of amniocentesis for prenatal diagnosis allows us to obtain cells for karyotyping, a method of identifying chromosomal characteristics within the cell. Through this method, selected abnormalities of a fetus can be diagnosed *in utero,* and therapeutic abortion can be carried out if necessary. It is the intent of this paper to review the state of the science and the art which allow us to provide prenatal diagnosis, and thereby genetic counseling.

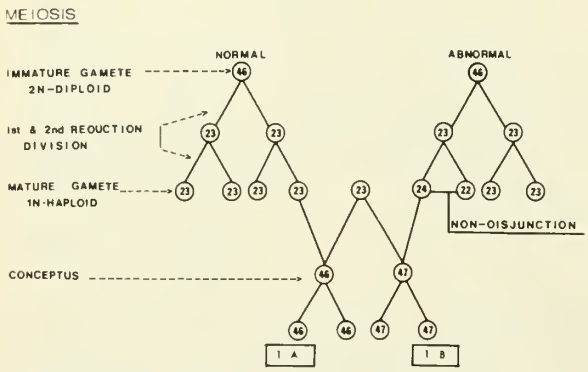

Figure 1 A—Meiosis or normal reduction division wherein the immature gamete containing 46 chromosomes (diploid number) is reduced to half that number, 23 (haploid number). **1 B**, Meiotic nondisjunction wherein there occurs a misdivision of chromosomes. The mature egg or sperm gains or loses a chromosome as a result of faulty segregation. Where union with the mate's gamete occurs, there is a net gain or loss of a chromosome (aneuploidy).

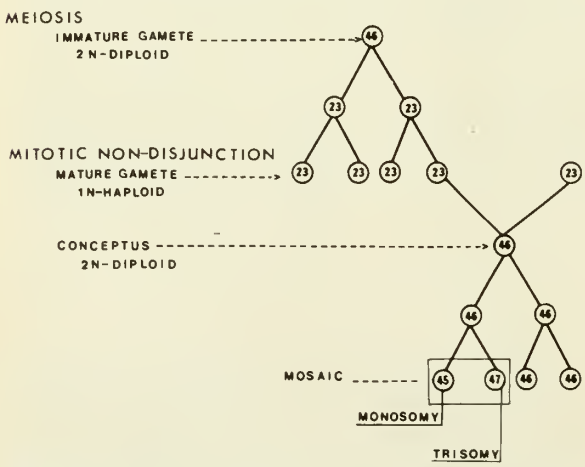

Figure 2.—Mitotic nondisjunction will result in a fetus with more than one cell line. An example is a child with Turner's phenotype and as in the illustration, having three cell lines, that is, 45XO/46XX/47XXX. If mitotic nondisjunction involves an autosome, the cells missing an autosome do not survive, thus leaving a fetus with two cell lines, that is, 46 and 47.

Because genetics was not commonly taught in medical schools before the late 1960's, a brief description of the modes of inheritance may be helpful in the subsequent discussion.

Genetic information is transmitted by a variety of mechanisms:

- Chromosome Inheritance,
- Gene Transmission (Mendelian Inheritance),
- Multifactorial or Polygenic Inheritance.

Chromosome Inheritance

A person's phenotype consists of his physical characteristics and personality traits, some of which are determined by his environment and some of which are determined by his genotype. The genotype is the total genetic endowment of the person. It is a general term that can refer to a specific gene locus or to the total chromosomal mass, including the number, size and arrangement of chromosomes in his cells. The somatic, or nonsex cells of the human body contain 46 chromosomes, which represent the diploid (2N) state. The sex cells, or gametes, contain half the number in the somatic cells, or 23 chromosomes, and constitute the haploid state (1N). It becomes

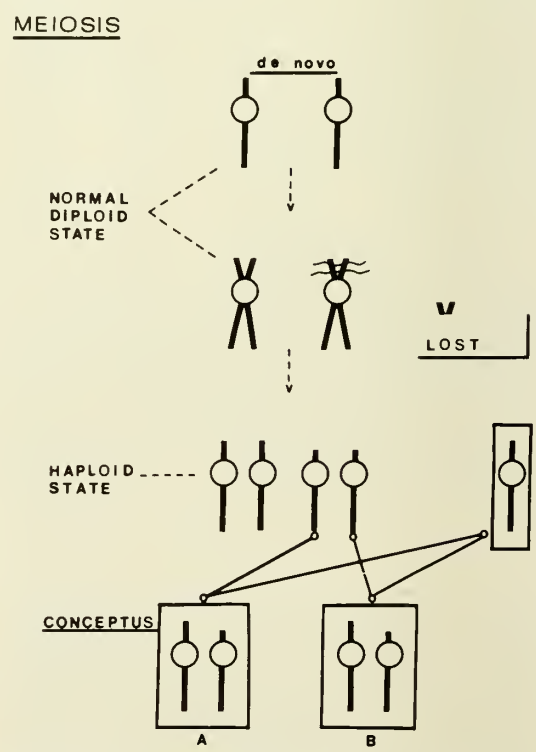

Figure 3.—Two breaks take place with loss of an acentric (without centromere) fragment. However, when this chromosome pairs with its homologue from the mate, one of a pair of chromosomes is missing a portion of the chromosomal mass.

clear why 23 chromosomes are contained in the gametes, for when the sperm and ovum fuse at conception, the total number of chromosomes present in the newly fertilized egg or zygote will then be 46, the number found in all normal somatic cells (Figures 1-3). This number of chromosomes is reduced only in the sex cells at meiosis, a specialized form of cell division. Regular cell division is termed mitosis, and proceeds to restore exactly 46 chromosomes to each daughter cell after every division, in normal cells. (The number, type, size and arrangement of chromosomes can be determined by karyotyping, whereby these chromosomal characteristics are shown.) However, in cases of genetic abnormality, the phenotype can be altered by numerical or structural changes, or both, in the chromosome complement (genotype).

Numerical abnormalities include monosomy X, as in Turner's syndrome; trisomies, as in Down's (G21), Edward's (E18) and Patau's (D13) syndromes; Klinefelter's syndrome (XXY); Triple X, and the like. Trisomies may also be complete or partial. Structural rearrangements of individual chromosomes produce varying effects, which may or may not be familial.

Numerical alterations in the chromosomal complement have their origin almost exclusively before conception, and probably during gametogenesis or meiosis. During meiosis, the chromosomes lie alongside each other, and exchange segments. Under normal conditions, these exchanges are balanced—that is, no chromosome is left with an extra fragment or is deprived of one. But in some instances, a chromosome is given an extra portion of chromosomal material, while another chromosome is shortened by the loss of a segment. This is known as translocation. In other cases, chromosomes that have joined to exchange genetic material fail to separate in time for cell division. This situation is known as nondisjunction, resulting in the loss or gain of a chromosome in the daughter cell (Figure 1 B). In the daughter cell with the extra chromosome, all its descendants will contain an extra chromosome, and thus the conceptus will be so characterized in a karyotype of its cells. Mitotic nondisjunction, or nondisjunction *after* fertilization can occur to produce mosaicism (Figure 2). In this situation, the monosomic cell does not survive (unless it is monosomy X); however, the embryo will survive, but this results in a mixture of normal and trisomic cells within the conceptus (mosaicism).

Structural rearrangements which have their origin during gametogenesis of the parent (de novo) (Figure 3) can produce a deletion syndrome that is not familial. The same genotype and phenotype can occur as a result of a balanced translocation that occurred before conception of the parent (Figure 6). An example of a chromosomal deletion is cri du chat syndrome, which

Figure 4.—Karyotype of a balanced D/G translocation. The individual (male) has the normal mass of chromosomal material; however, two chromosomes have joined (a D and a G) to produce an abnormal number of chromosomes.

can occur as a de novo chromosome abnormality, or as a result of translocation. Two types of translocations can occur—and they may be balanced or unbalanced, involving one or several types of chromosomes—which result in (1) robertsonian translocation, or centric fusion, and (2) reciprocal translocation. The robertsonian translocation, or centric fusion, is the joining of two acrocentric chromosomes. In the balanced state, though numerically lacking one chromosome, the chromosomal mass in the nucleus is normal (Figure 4). The result is a phenotypically normal person; however, that person would be at high risk for producing a child with an unbalanced robertsonian translocation. In the unbalanced state, there is an extra chromosomal mass, and this is responsible for the production of phenotypic alterations. This is the mechanism that causes familial varieties of Down's syndrome (Figure 5).

In reciprocal translocation, the modal number of chromosomes usually remains at 46, but fragments of chromosomal material are exchanged between two nonhomologous chromosomes (Figure 6). In the balanced state, the chromosome morphology may not be normal; however, the normal amount of chromosomal material is still present. If in reduction division, however, a structurally rearranged chromosome is given to that offspring, then that offspring may receive an excess or loss of chromosomal material. This is responsible for a host of phenotypic alterations, and actually, although the reciprocal translocation can occur between any two chromosomes, structural rearrangements of large chromosomes are rare.

Deletions may also occur as a result of a mutation in the gamete of a parent before the conception of the infant, and affect only that particular gamete (de novo). The latter does not indicate that the parents will be at high risk in the future because generally only a single gamete has been altered. However, when the deletion results from a balanced translocation in the parent, all cells of the parent's body are involved, including the gametes, and the parents are at high risk for an abnormality in the fetus with each pregnancy.

Chromosome inversions represent another event that may affect the phenotype. An inversion results when a chromosome breaks in two places (or more) and the two distal fragments rejoin the midsection in inverted order (Figure 7). Since the genes will then be in the wrong order, it is postulated that any proteins coded by these rearranged genes will be different from the ones that should have been made, had the chromosomes been in their proper order. The zygote, and ultimately the infant, may suffer structural or biochemical abnormalities as a result of altered gene order, and hence gene function.

Inversion, by disturbing gene sequence, may also interfere with normal pairing at meiosis, including the process of crossing-over between pairs

Figure 5.—An unbalanced robertsonian translocation, wherein the fetus received the normal number of chromosomes from both parents. A D chromosome from one parent carries an extra G chromosome attached to the top of the D, producing a trisomy in that male child. Even though the correct number of 46 chromosomes was present, the mass of 47 chromosomes is still present.

of homologous chromosomes. The end result may be the loss or gain of all or part of a chromosome in that gamete. After the defective and normal gametes combine (conception), the resulting zygote will develop into a person who, also, may suffer from severe abnormalities due to chromosomal rearrangement.

Mendelian Inheritance

There are approximately 1,700 known diseases[1] that are proven or suspected to be due to mendelian inheritance. These diseases are transmitted primarily in an autosomal recessive, autosomal dominant, X-linked recessive or X-linked dominant mode of inheritance. Y-linked inheritance is very rare, if it ever occurs. The Y chromosome represents the sex determining chromosome, which when present generally results in the male phenotype.

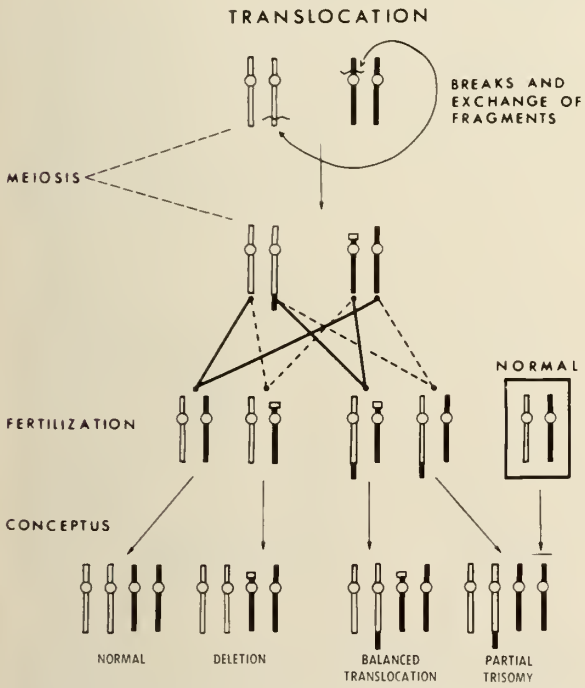

Figure 6.—Reciprocal translocation includes exchanges of fragments between two chromosomes. As a result, there occurs a balanced translocation which can pass the same chromosome abnormality onto its offspring. The carrier of a balanced translocation can produce a genotypically normal child with a chromosome deletion or a partial trisomy.

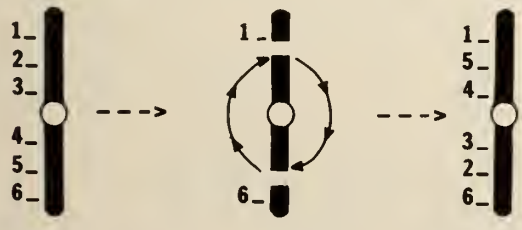

Figure 7.—Chromosome inversion occurs when a single chromosome suffers two breaks. A segment of the chromosome may then be altered 180 degrees from its original structure (thus sequence). This phenomenon alone may alter gene function, but it may also interfere with normal pairing at meiosis.

Autosomal recessive inheritance criteria (see Figure 8) include the following factors:

- Most people affected are the children of apparently normal parents.
- Often more than one child in a sibship is affected; on the average a quarter of the sibs of the proband are affected.
- Both sexes are equally affected.
- Affected people who mate with normal people have apparently normal children.
- In rare recessive cases, there is an increased incidence of consanguinity. Other examples include most inborn errors of metabolism, such as phenylketonuria and Tay-Sachs disease. Sickle cell disease is also due to autosomal recessive inheritance. Again, the heterozygote (or carrier) is asymptomatic, for the normal gene is dominant over the mutant gene. However, when heterozygous parents mate they face each pregnancy with a 25 percent chance of having a child who is genotypically homozygous, thus phenotypically abnormal.

Criteria for autosomal dominant inheritance (Figure 9) include:

- Every affected person has one affected par-

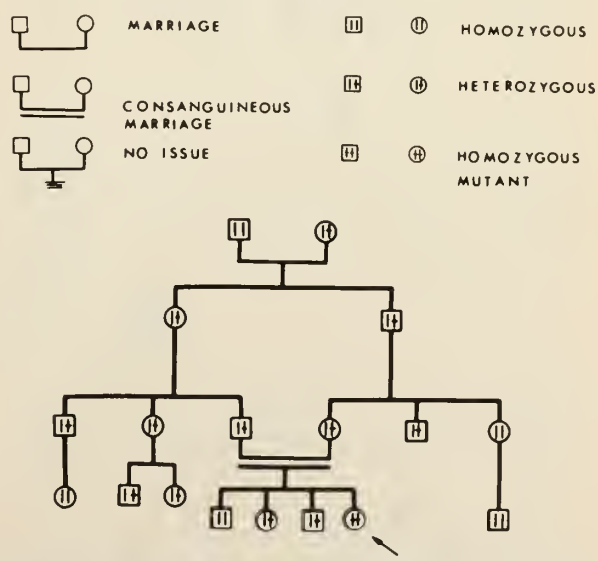

Figure 8.—Pedigree of a child with a genetic (autosomal recessive) variety of microcephaly.

ent, unless the abnormal gene was the result of a mutation.

- Affected heterozygous people mating with normal people have, on the average, equal numbers of normal and affected children.
- The sexes are equally affected.
- Normal family members do not transmit the abnormality to their children. In this situation, the abnormal gene is dominant over the normal gene. Many of the autosomal dominant disorders, however, present with structural malformations that clinically are not as disabling as the more biochemically and globally involved autosomal recessive and X-linked recessive disorders.

Criteria for X-linked recessive inheritance (Figure 10) include:

- Affected fathers do not transmit the mutant gene to their sons, but transmit it to all their daughters who are then heterozygous (carriers).
- Heterozygous mothers transmit the genes to half their sons, who are enzyme deficient, and to half their daughters, who are then heterozygous.
- Homozygous mothers transmit the gene to all their sons who will then be enzyme deficient.

Criteria for X-linked dominant inheritance (Figure 11) include:

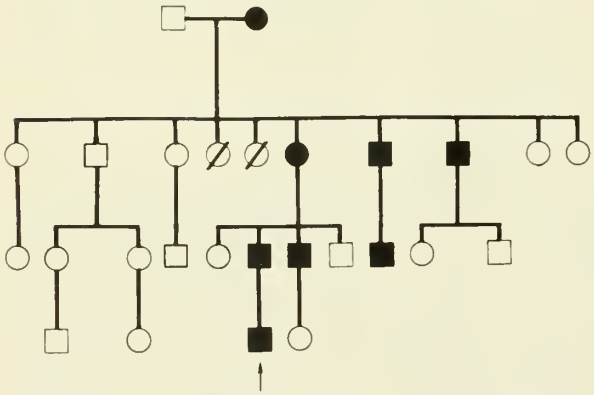

Figure 9.—Pedigree of a family with Huntington's chorea.

- Affected males transmit the trait to all their daughters and to none of their sons.
- Transmission by females follows the same pattern as autosomal dominant inheritance.
- In rare X-linked dominant disorders, affected females are twice as frequent as affected males. In this case, the father with X-linked disease transmits the disorder only to his daughters, whereas the heterozygous mother passes the trait on to 50 percent of her offspring, and the homozygous on to 100 percent of hers, regardless of sex.

Multifactorial Inheritance

Multifactorial inheritance is responsible for such traits as height, skin color, blood pressure and intelligence. This mode of inheritance is also responsible for the transmission of a large variety of structural malformations, such as spina bifida cystica (SBC) with meningomyelocele, cleft lip/cleft palate and club foot. Multifactorial implies an interrelationship between the environment and the genome in the transmission of normal characteristics or of disease states. This interrelationship is clearly established in twin studies. Let us assume that Q syndrome is purely a genetic disorder. Given that assumption, when Q syndrome occurs in twins with the same genome (MZ twins), both twins will always have the same syndrome. But if Q syndrome occurs in twins who do not have the same genome (DZ twins), then concordance for Q syndrome would be no more common than in siblings. If Q syndrome were purely environmental, the incidence of Q syndrome would be very similar in MZ and DZ twins. Disorders of multifactorial inheritance are not primarily genetic or environmental in origin but are primarily a product of their interaction. Cleft lip/cleft palate (CL/CP) shows this interaction. Concordance in MZ twins is much greater than in DZ twins. This implies that even though

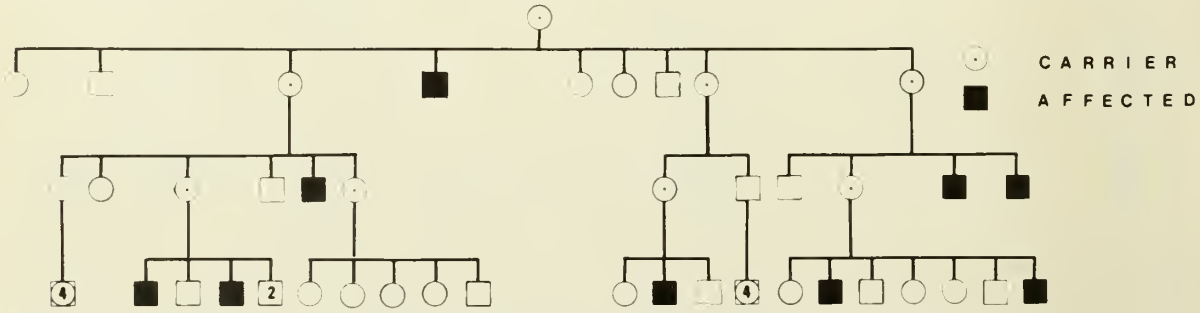

Figure 10.—Pedigree of a family with Duchennes' pseudohypertrophic muscular dystrophy. Other X-linked recessive disorders include hemophilia and Lesch-Nyhan syndrome.

the genome is identical as in MZ twins, the effect of a teratogen upon that genome may vary. However, the more similar the genome, the more likely it is that the end result (in this instance, CL/CP) will be the same, whereas the effects of a teratogen upon persons with a relatively dissimilar genome (DZ twins) will have less reproducible effects. This empirical observation implies genetic forces have a powerful influence over the ultimate results of an environmental insult. Persons with an identical genome (MZ twins) react in a more predictable fashion to the same environmental insult than do those with a relatively dissimilar genome (DZ twins). Cleft lip (with or without cleft palate) occurs in one of 1,200 infants. However, where one of monozygotic twins is affected, the other will be affected four times out of ten, about 400 times the chance expectation of the general population.[2]

Congenital hip dislocation is another multifactorial disorder.[2] In the general population, it occurs in one of 2,000 infants; however, when it occurs in the sibling, the risk in the other sib is found to be closer to 4 percent. Congenital hip dislocation is characterized by two factors: (1) a shallow acetabulum with an abnormally developed femoral head (genetic) and (2) physical relationship of the femoral head to the dysplastic acetabulum (environmental). Study of varying ethnic practices in child rearing provides an example of environmental influences on multifactorial disorders. Lapp infants who have congenital hip dysplasia and who are swaddled with their hips tightly adducted, have a much higher incidence of hip dislocation than do infants in some Chinese or Indian cultures where they are carried in "backslings" which hold their legs flexed and abducted, and therefore keep the head of the femur in the proper approximation to the acetabulum.

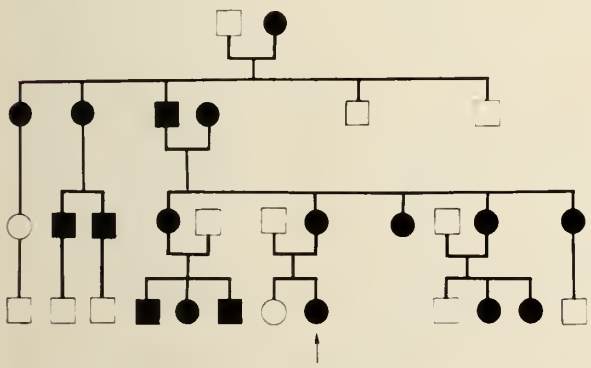

Figure 11.—Pedigree of a family with nephrogenic diabetes insipidus, an X-linked dominant disorder. Note the excess of females with the disease in contrast to the affected males.

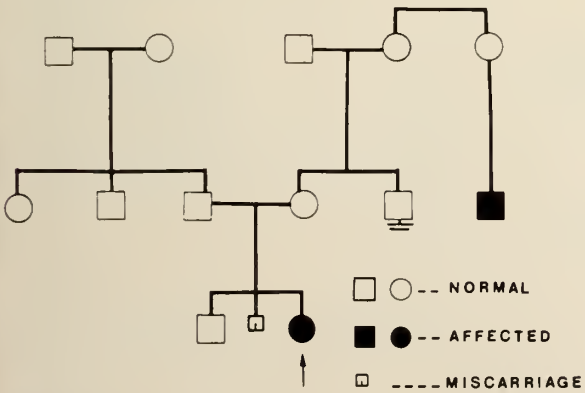

Figure 12.—A pedigree showing a family with two affected children, the proband with spina bifida cystica and a second cousin who dies at birth due to anencephaly. Miscarriage before an affected child with spina bifida occurs more than as a random event.

Characteristics of multifactorial inheritance (Figure 12) include:

- The further the relative from the clinical case, the less likely that relative is to have the disease.
- The more severe the disease, the higher risk to relatives.
- If sex differential is present, and the disease occurs in the opposite or resistant sex, the higher the risk to relatives.
- The more common the disease, the more closely the recurrence risk resembles that of the general population sample.

Prenatal Diagnosis and Genetic Counseling

Genetic counseling is the delivery of professional advice concerning the magnitude of, the implications of and the alternatives to dealing with the risks of occurrence of an hereditary disorder within a family. Prerequisites for the provision of genetic counseling include (1) accurate anatomic and etiologic diagnosis and (2) knowledge of the mode of inheritance regarding the disorder in question, as well as knowledge of the recurrence risk.

Recently, a couple was seen whose case represents a tragic failure to heed these two prerequisites. Three years before, at the age of 29, the mother was delivered of a child with Down's syndrome associated with 47 chromosomes. This indicated a sporadic event, but nevertheless did increase her risks in subsequent pregnancies. Nonetheless, she was informed by two physicians that

TABLE 1.—*Congenital Abnormalities That Can Be Detected* In Utero*

Disorders	*Deficient enzyme activity or other features in tissues or cultured fibroblasts*	*Prenatal diagnosis*	*Useful tissue for postnatal heterozygote detection*
Amino Acid and Related Disorders			
Argininosuccinic aciduria	argininosuccinase	made	skin, fibroblasts
Citrullinemia	argininosuccinic acid synthetase	made	fibroblasts
Cystathionuria	cystathionase	potentially possible	plasma, urine
Cystinosis	intracellular cystine accumulation	made	fibroblasts
Histidinemia	histidase	possible	possible fibroblast
Homocystinuria	cystathionine synthetase	possible	fibroblasts
Hyperammonemia (Type II)	ornithine transcarbamylase	possible	uncertain
Hyperlysinemia	lysine-ketoglutarate reductase	potentially possible	fibroblasts
Hypervalinemia	valine aminotransferase	potentially possible	fibroblasts
Ketotic hyperglycinemia	propionyl CoA carboxylase	possible	fibroblasts
Maple syrup urine disease:			
a. severe infantile	branched chain keto acid decarboxylase	made	fibroblasts
b. intermittent	as above	possible	fibroblasts
Methylmalonic Aciduria:			
a. unresponsive to vitamin B_{12}	methylmalonyl CoA mutase	made	fibroblasts
b. responsive to vitamin B_{12}	deoxyadenosyl-B_{12} synthetase	possible	leukocytes, fibroblasts
Ornithemia	ornithine-α-keto acid aminotransferase	made	fibroblasts
Disorders of Carbohydrate Metabolism			
Glycogen-storage disease (Type II)	α-1, 4-glucosidase	made	leukocytes, fibroblasts
Glycogen-storage disease (Type III)	amylo-1, 6-glucosidase	possible	leukocytes
Glycogen-storage disease (Type IV)	branching enzyme	made	fibroblasts
Galactosemia	galactose-1-P uridyl transferase	made	red blood cells, fibroblasts
Galactokinase deficiency	galactokinase	possible	fibroblasts
Pyruvate decarboxylase deficiency	pyruvate decarboxylase	potentially possible	fibroblasts
Glucose-6-PO_4 dehydrogenase deficiency	G-6-PO_4 dehydrogenase	potentially possible	fibroblasts
Mucopolysaccharidoses			
Hurler's syndrome	α-L-idurono	made	fibroblasts
Hunter's syndrome (X-linked recessive; all others autosomal recessive)	α-L-idurono-sulfate sulfatase	made	fibroblasts
Sanfilippo syndrome A&B	A-Heparitin sulfate sulfatase	made	fibroblasts
	B-α-Acetylglucosaminidase	made	fibroblasts
Morquio's syndrome	unknown	potentially possible	fibroblasts
Scheie's syndrome	α-L-idurono	possible	fibroblasts
Maroteaux-Lamy syndrome	unknown	potentially possible	fibroblasts
I-cell disease	reduced activity of multiple lysosomal enzymes in cultured fibroblasts	made	fibroblasts
Fucosidosis	α-L-fucosidase	possible	fibroblasts
Mannosidosis	α-mannosidase	possible	fibroblasts
Disorders of Lipid Metabolism			
General gangliosidosis (G_{M1} gangliosidosis Type I)	β-galactosidase B and C	made	fibroblasts
Juvenile G_{M1} gangliosidosis (G_{M1} gangliosidosis Type II)	β-galactosidase B and C	possible	fibroblasts

TABLE 1.—*Congenital Abnormalities That Can Be Detected* In Utero *(Continued)*

Disorders	*Deficient enzyme activity or other features in tissues or cultured fibroblasts*	*Prenatal diagnosis*	*Useful tissue for postnatal heterozygote detection*
Sandhoff's disease (G_{M2} gangliosidosis Type II)	hexosaminidase A and B	made	serum, leukocytes, fibroblasts
Juvenile G_{M2} gangliosidosis (G_{M2} gangliosidosis Type III)	partial deficiency of hexosaminidase A	possible	serum, fibroblasts
Tay-Sachs disease G_{M2} gangliosidosis Type I)	hexosaminidase A	made	serum, leukocytes, fibroblasts
Neimann-Pick disease	sphingomyelinase	made	fibroblasts
Gaucher's disease	glucocerebroside β-glucosidase	made	fibroblasts
Metachromatic leukodystrophy	arylsulfatase A	made	fibroblasts
Lactosyl ceramidosis	lactosylceramide β-galactosidase	potentially possible	fibroblasts
Wolman's disease	acid lipase	potentially possible	fibroblasts
Fabry's disease	ceramidetrihexoside	made	fibroblasts
Refsum's disease	phytanic acid α-hydroxylase	possible	fibroblasts
Krabbe's disease (globoid cell leukodystrophy)	β-Galactocerebrosidase	made	serum, leukocytes, fibroblasts
Miscellaneous Disorders			
Acatalasemia	catalase	potentially possible	fibroblasts
Chediak-Higashi syndrome	unknown	potentially possible	fibroblasts
Congenital erythropoietic porphyria	uroporphyrinogen III synthetase	potentially possible	fibroblasts
Lesch-Nyhan syndrome (X-linked recessive; all others autosomal recessive)	hypoxanthine-guanine phosphoribosyl transferase	made	fibroblasts
Lysosomal acid phosphatase deficiency	lysosomal acid phosphatase	made	fibroblasts
Orotic aciduria	orotic acid phosphoribosyl transferase; orotidylic decarboxylase	potentially possible	fibroblasts
Xeroderma pigmentosum	deoxyribonucleic acid (DNA)-repair endonuclease	potentially possible	fibroblasts
Chromosome Abnormalities			
D Trisomy (Patau's syndrome)	.....	all detectable or are potentially so	.....
E Trisomy (Edward's syndrome)	.....	"	.....
G Trisomy (Down's syndrome)	.....	"	.....
B Deletion		"	.....
4—Wolf's syndrome	.....	"	.....
5—Cri du chat syndrome	.....	"	.....
E 18	.....	"	.....
XO (Turner's syndrome)	.....	"	.....
XXY (Klinefelter's syndrome)	.....	"	.....
XXX	.....	"	.....
XYY	.....	"	.....
Dysmorphic Syndromes			
Midline defects of back (spina bifida cystica and anencephaly)	.....	α-fetoprotein	.....
T.A.R. (thrombocytopenia and absent radius)	.....	fetal x-ray study	.....
Microcephaly	.....	sonogram	.....
Polycystic disease of kidney	.....	sonogram	.....

*Adapted from Milunsky, et al.[5]

in subsequent pregnancies there was little chance that her children would have Down's syndrome. In 1973 at the age of 30, she was delivered of a second child with Down's syndrome, again with 47 chromosomes. She is again pregnant and her pregnancy will be monitored with amniocentesis. The parents, feeling their responsibilities, care for the two affected children, and this has resulted in severe emotional distress for the mother. Emotional strain on members of the family is evident, and has even resulted in completely unfounded accusations that the mother is having an affair with another man. And to compound the situation, when the mother sought counseling from her church she was told she would go to hell because of considering abortion in the current pregnancy. To prevent such tragic situations as this family's plight, the medical profession must use the expertise of medical geneticists.

Those families who would benefit by genetic counseling include those in which any of the following is present:

- Known chromosomal disorders,
- Known disorders due to mendelian inheritance,
- Mental retardation of unknown origin,
- Failure of sexual maturation or failure of sexual development,
- Congenital malformations,
- Floppy infant syndrome or
- Leukemia.

In order to avoid misinformation, a genetic counselor must fulfill additional requirements. These include:

- Knowledge and insight into variations of disease, including possible therapy and prognosis;
- Knowledge of methods to determine the carrier state;
- Knowledge of methods and risks of therapeutic abortion, problems of adoption, artificial insemination and the risks of procedure versus the risks of the disease, and
- Experience and sensitivity in counseling.

If amniocentesis is to be utilized for a prenatal diagnosis, there must be an identifiable cell marker, either an abnormal karyotype or the biochemical expression of an abnormal gene. X-ray studies, sonograms and perhaps fetoscopy can also be useful in prenatal diagnosis. Prenatal diagnosis should be available to any family at an increased risk for an abnormal child because of maternal age or a known genetic abnormality in the family. Amniocentesis should not be denied because a family has not reached a decision regarding abortion. Exposure to those few known teratogens or to ionizing radiation may raise questions in the family's or in the primary physician's mind as to the possible effects on the fetus. In cases like these the geneticist's opinion may be of value in dispelling false notions and in estimating risks.

Prenatal diagnosis, including genetic counseling, is indicated in the following cases:[3]

- *High-risk families* (one in 20 or greater). These include families with autosomal recessive disease, families with X-linked recessive disease and families with translocation carriers.
- *Families with a moderate risk* (one in 40 or greater). These include families in which the mother is 40 years of age or older and families with a previous child born with a midline defect of the back (anencephaly or spina bifida associated with meningomyelocele or meningocele).
- *Families with a low risk* (less than one in 40). These include families in which the mother is 35 years of age and families with a previous child born with a chromosomal abnormality.

Before amniocentesis is carried out, the use of ultrasound[4] is recommended for (1) placental and fetal localization, (2) detection of undiagnosed twins and (3) confirmation of gestational age. At the time of amniocentesis, 25 to 30 ml of sterile amniotic fluid should be submitted to the laboratory immediately, but at most within 24 hours after obtaining the fluid. The procedure is optimally done at the beginning of the *16th week* because before that time it is difficult to obtain sufficient fluid. At a later time, there is time pressure if a decision is to be made in favor of therapeutic abortion (by the 20th week). This stems from the fact that four weeks must be allowed for the optimum number of laboratory studies to be done. Some disorders that are currently detectable prenatally are shown in Table 1.

Before amniocentesis is done, the counselor must discuss with both parents a number of issues. How badly they wish to have another child can only be assessed in relation to their family size, the presence or absence of obstetrical problems, their avowed feelings and their religious background. What their attitudes are toward interruption of pregnancy and the strength of their relationship will also have a significant bearing on their decision to allow the pregnancy to continue to term. The parents should under-

stand the risks of the procedure. When carried out by an experienced and qualified obstetrician, injury to the fetus from amniocentesis (including puncture wounds and fetal hemorrhage) and hemorrhage or infection in the mother occur in less than 1 percent of cases.[5] Spontaneous abortion accounts for most complications, and at present it is uncertain whether the abortion of such cases is caused by the amniocentesis. Fetal and maternal morbidity are negligible, and account for but a fraction of the 1 percent complications.[6] Amniocentesis is not a procedure that should be done on an occasional basis. There should be close association between obstetrician, pediatrician, family practitioner and genetic counseling team. When one cannot deal with absolutes, the best possible approximation of risks must be provided and explained to the family.

Genetic counselors should be nonjudgmental and impartial, and must exert every effort to provide the family with all pertinent knowledge and implications for the decision regarding amniocentesis and possible subsequent therapeutic abortion. Neither the counselor nor the physician should impose his or her own values on any counselee. A typical question posed by parents confronted with the possibility of having a defective child is "Doctor, what would you do?" It is tempting to answer this question, a temptation which *must* be resisted. It is not the physician's place to tell parents what they should do. They should be aided in making a decision, and supported by the physician in their decision. It must be remembered that parents faced with the possibility of having a defective child are vulnerable to the spoken or unspoken value judgments of those professionals with whom they first come in contact. In our own personal professional lives, we might not choose to keep a severely flawed child in our homes, be it an infant with Down's syndrome or meningomyelocele or another disorder, but that is *not* our decision to make for others. We must take the time to find out what they, the parents, wish to do, and then help them cope with the ensuing problems. Giving parents or patients unwelcome, tragic and disastrous information is never pleasant, and is painful to the counselor. If a physician does not wish that type of emotional pain, which is a perfectly valid decision, then he should seek the consultation of those in medical genetics who can accept it.

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Molecular Pathology of the Thalassemia Disorders

Sixth Annual Paul M. Aggeler Memorial Lecture

Delivered October 7, 1975, San Francisco General Hospital

DAVID J. WEATHERALL, MD, *Oxford, England*

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. WALLERSTEIN:* *This year we have a bit of a departure from the usual Paul Aggeler Lecture. In the past, we have always presented either a colleague of Paul or a coagulationist. Paul, who so deeply touched all of us who worked with him and who served as the conscience of the School of Medicine, was profoundly interested in the scientific welfare of the San Francisco General Hospital. In the last two years, the intensity of progress in hematology at San Francisco General Hospital has shifted from coagulation to the field of thalassemia, so it became relatively easy to pick this year's speaker. Our Dean, who is a personal friend of Dr. Weatherall, will introduce him.*

DR. KREVANS:† Thank you very much, Ralph. It is a delight two years in a row to have the privilege of introducing the Aggeler Lecture. Last year, I had the privilege of introducing the late Dr. Judith Pool, who was a personal friend and with whom I spent many happy hours in study sections and on airplanes. This year it is a privilege to introduce David Weatherall. I met David in Baltimore more years ago than I suspect either of us would like to recall. He was one of a group of Liverpudlians who invaded the Johns Hopkins Medical School, almost all of whom have gone on to very distinguished careers in academic medicine.

David graduated from Liverpool, trained in medicine at the University of Liverpool, and then was volunteered by Her Royal Highness to go to Malaya in the service of his Queen. While in Malaya he continued his academic work, starting a career in the study of genetically determined abnormalities of hemoglobin. He came to Hopkins as a Fellow in genetics, and as we did with a couple of other people, we diverted him to hema-

*Ralph O. Wallerstein, MD, Chief of Clinical Hematology Division of the Medical Service, San Francisco General Hospital, Clinical Professor of Medicine and Clinical Pathology and Laboratory Medicine, University of California, San Francisco, and Chairman of the Paul M. Aggeler Memorial Committee.

†Julius R. Krevans, MD, Dean of the School of Medicine and Professor of Medicine, University of California, San Francisco.

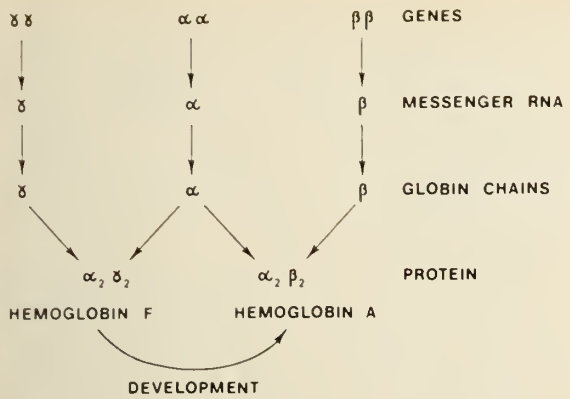

Figure 1.—Genetic control of human hemoglobin.

tology where he has remained ever since, although he still carries substantial credentials as a geneticist. He returned to Liverpool to finish his clinical training, and then returned to Baltimore for two years as a Postdoctoral Fellow in the laboratory, where we spent many happy hours discussing British history, United States history and occasionally hemoglobin abnormalities. He returned to Liverpool, and then recently was brought to Oxford University as a Nuffield Professor of Clinical Medicine and a Fellow of Magdalen College. So without further ado, it gives me great pleasure to introduce David Weatherall to you.

DR. WEATHERALL:* When I received your kind invitation to give this lecture, I already knew a great deal about the work of Paul Aggeler in hematology and coagulation, but I knew nothing about him as a person. It was a happy coincidence that just before I came we had a visitation in Oxford from Maxwell Wintrobe,† from whom I learned a great deal about Paul Aggeler the person, who had been a longstanding friend of his. With both of these sources of knowledge, I feel very honored that you have invited me to give this talk and I am absolutely delighted to be here.

In 1925 a rather obscure Detroit pediatrician, Thomas B. Cooley, first described the disease of thalassemia in a few children in that city, and a few years later the term thalassemia was coined because they thought that all of these children must have come from the Mediterranean. Then a tremendous hiatus of about 25 years occurred, owing to the war and language problems in the Italian and English literature, before the realization that this was a genetic disease. Then there was another gap; even ten years ago thalassemia was still in small print in most general medical textbooks. It is really only in the last few years that we have realized that this is probably the most common genetic disease, or group of genetic diseases, resulting from a single gene abnormality to cause a major world health problem. In fact, the incidence of the disease in the world population is rather staggering. For example, in just one country, Thailand, with a population of around 35 million, it is estimated that about 400,000 to 500,000 children will have one of the forms of thalassemia sufficiently severe to require medical treatment, in many cases repeated blood transfusions. It is also a massive problem in parts of Italy and other Mediterranean regions, and I think it will become such in India and Pakistan once the problems of nutritional anemia and infection are overcome there. Thus it is a widespread clinical problem, and it is now clear that it is a very heterogeneous group of diseases. The other interesting feature is that studying thalassemia tells us much about other genetic disorders since it provides the chance to study diseases in which there is a reduced rate of protein synthesis.

When we talk about thalessemia, we have to talk mainly of a genetic disorder of hemoglobin synthesis. For those of you who are not living with globin chains every day, I thought I should review what we know about the genetic control of hemoglobin synthesis.[1] Figure 1 shows what one might call the poor man's guide to hemoglobin synthesis and a simplified model of what happens during normal human development when one switches from fetal hemoglobin, which one has had throughout intrauterine life, to adult hemoglobin. One has to make a molecule that in adult life has two alpha chains and two beta chains, whereas in fetal life it has two alpha chains and two gamma chains. Throughout development hemoglobin production is continuous, and alpha chains combine with gamma chains in fetal life and with beta chains in adult life. This beautifully controlled switch occurs mainly late in fetal maturation, but it also occurs partially in the early fetal stages. As we will see later this is important for antenatal diagnosis. We will be looking at the genetic disorders at the loci controlling the alpha and beta chains of human hemoglobin. Furthermore, we must examine the heterogeneity of human hemoglobin because we do not have just adult and fetal hemoglobins, as simplified above,

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†Maxwell M. Wintrobe, MD, Director of the Cardiovascular Research and Training Institute and Distinguished Professor of Internal Medicine, Utah Medical Center, Salt Lake City.

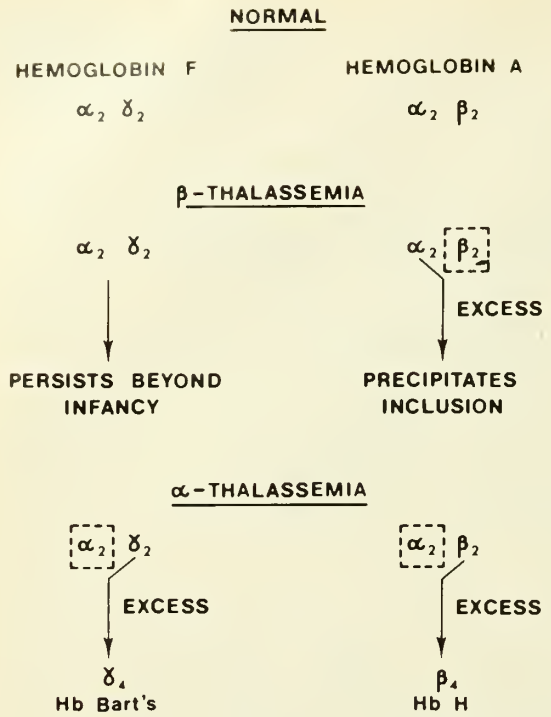

Figure 2.—The thalassemias; a general classification. Hb = hemoglobin.

but a number of other hemoglobins. Forget about embryonic life, it is not pertinent to the molecular pathology of the thalassemia disorders and even Dr. Kan* is not looking for thalassemia in embryos yet.

Figure 2 shows a reasonably current version of the genetic control of human hemoglobin in fetal and adult life. Of course, normal adults have in addition to a major component, a minor component of alpha chains and delta chains. Dr. Schroeder's† group in working with the gamma chain sequences found that all of us have two species of fetal hemoglobin, one with glycine at position 136 in the gamma chain and one with alanine, and that these two types of fetal hemoglobin are the products of two separate gene loci. Thus we have marked them as G gamma and A gamma. There are two alpha chain loci on each chromosome, not one as depicted in Figure 1, and probably one beta locus and one delta locus. Looking at this model, we can classify the genetic diseases of this system into three main groups: structural hemoglobin variants, which produce clinical disorders only if they alter the stability or function of the hemoglobin; the thalassemias, which are really a group of disorders in which there is a reduced rate of synthesis of one or more of the globin chains, and finally, a developmental abnormality in which some people, for presumably genetic reasons, do not switch from fetal to adult hemoglobin production but continue to make fetal hemoglobin.

Here we are concerned with the group of thalassemic disorders in which the rate of synthesis of one or more of the adult types of globin chains is reduced. We can broadly classify the thalassemias as Drs. Ingram‡ and Stretton§ did in the late 1950's into two forms; the alpha-thalassemias and the beta-thalassemias, as shown in Figure 2.

In beta-thalassemia there is a genetic defect in beta chain production, which then results in excess production of alpha chains. If there are too many alpha chains in a cell, they cannot form a viable hemoglobin, so this material precipitates and forms an inclusion body. This form of beta-thalassemia is also associated with persistent fetal hemoglobin production.

In alpha-thalassemia, of course, fetal or adult hemoglobin is not made adequately, and thus there is either an excess of gamma chains, called hemoglobin Bart's, or an excess of beta chains, called hemoglobin H. Alpha-thalassemia then is a condition in which there is a defect in alpha chain production in adult life resulting in hemoglobin H and a defect in alpha chain production in fetal life producing hemoglobin Bart's. However, it is not quite so simple because both of these disorders are heterogeneous. Table 1 shows that there are many types of alpha-thalassemia. There are three main alpha-thalassemias that have a high frequency in the world population: the bad one, alpha-thalassemia-1; the not-so-bad one, alpha thalassemia-2 and a structural hemoglobin variant, Constant Spring, that occurs with an extremely high frequency in some populations and results in clinical features of alpha thalassemia. Thus the homozygote with α-thalassemia-1 (the bad one) dies *in utero* with hydrops fetalis; a homozygote with α-thalassemia-2 (the milder one) is not very sick and has clinical features similar to thalassemia minor, and a double heterozygote with a combination of the severe and the mild forms results in a fairly severe deficit

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†Walter A. Schroeder, PhD, Research Associate, California Institute of Technology, Pasadena.

‡Vernon M. Ingram, PhD, DSc, Professor of Biochemistry, Massachusetts Institute of Technology, Cambridge.

§Antony O. W. Stretton, PhD, Department of Zoology, University of Wisconsin, Madison.

TABLE 1.—*The Alpha-Thalassemias*

Thalassemia	*Homozygote*	*Heterozygote*
α-thal-1	Hemoglobin Bart's hydrops, 80% hemoglobin Bart's	Thalassemia minor, 5-10% hemoglobin Bart's at birth
α-thal-2	Thalassemia minor, 5-10% hemoglobin Bart's at birth	Thalassemia minor or silent, 1-2% hemoglobin Bart's at birth
Hemoglobin Constant Spring	Thalassemia minor, 5-6% hemoglobin Constant Spring	Silent, 0.5-1% hemoglobin Constant Spring
Hemoglobin Icaria	Not described	? Silent, 0.5-1% hemoglobin Icaria
Hemoglobin Koya Dora	Not described	? Silent, 0.5-1% hemoglobin Koya Dora
Hemoglobin Q	Not described	? Silent, hemoglobins $A+Q+A_2+Q_2$

TABLE 2.—*The Beta-Thalassemias*

Thalassemia	*Homozygote*	*Heterozygote*
β thal$^+$	Cooley's anemia, hemoglobins $A+F+A_2$	Thalassemia minor, raised hemoglobin A_2
β thal$^+$ (Negro)	Thalassemia intermedia, hemoglobins $A+F+A_2$	Thalassemia minor, raised hemoglobin A_2
β thal$^+$ (High F)	Thalassemia intermedia, hemoglobins $A+F+A_2$	Thalassemia minor, 5-12% hemoglobin F, raised hemoglobin A_2
β thal^0	Cooley's anemia, hemoglobins $F+A_2$	Thalassemia minor, raised hemoglobin A_2
β thal^0 (Ferrara)	Cooley's anemia, hemoglobins $F+A_2$	Not described in detail
($\delta\beta$) thal^0	Cooley's anemia, hemoglobin F only	Thalassemia minor, hemoglobin F 5-15%, hemoglobin A_2 normal
$\delta\beta$ thal$^+$ (silent)	Not described	Minimal blood changes, normal hemoglobins F and A_2
$\delta\beta$ Lepore	Cooley's anemia, hemoglobins F+ Lepore	Thalassemia minor, hemoglobin A+ Lepore, $+A_2$
Excess α-chain production	Not described	Thalassemia intermedia, +inclusion bodies, raised hemoglobin A_2
Hemoglobin K Woolwich	Not described	Thalassemia minor, hemoglobins A+K, raised hemoglobin A_2

Figure 3. — Children with beta-thalassemia and hemoglobin E-thalassemia.

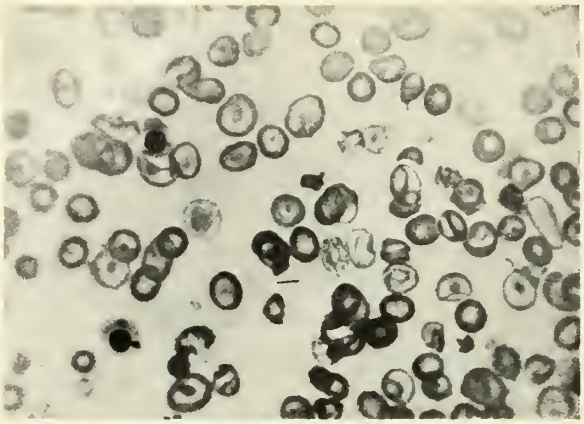

Figure 4.—Blood smear from a homozygous beta-thalassemic (Wright's stain; reduced from original magnification × 1,000).

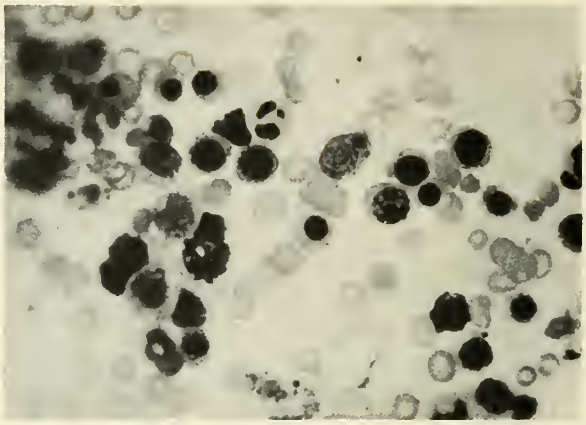

Figure 5.—Bone marrow from a homozygous beta-thalassemic (Wright's stain; reduced from original magnification × 1,000).

of alpha chains and a condition called hemoglobin H disease.

Table 2 shows that there are many types of beta-thalassemia, but for our purposes they can be divided into beta^{+}-thalassemia and beta^{0}-thalassemia. People with beta^{+}-thalassemia make beta chains but at a reduced rate, and people with beta^{0}-thalassemia make no beta chains. The subtypes need not concern us here.

The clinical picture of homozygous beta-thalassemia, either "+" or "0", is probably familiar to most of you. Figure 3 shows some Thai children with beta-thalassemia. They are anemic from the first year or even months of life; many of them require regular blood transfusions to survive; they are stunted in growth, have skeletal deformities and develop massive hepatosplenomegaly. In the United States one does not usually see a badly neglected person with thalassemia, but a child who is not being transfused and is in the first year or two of life with only 1 or 2 gm of hemoglobin per dl looks as if he or she has a malignant disease. It is a hypermetabolic state; the children are wasted and pot-bellied owing to the big spleen, and hyperuricemia and a continuous fever develop. The striking feature of this disease is that it is a proliferative disorder resulting from a primary defect in beta chain production.

If we look at a peripheral blood smear from a patient with thalassemia, shown in Figure 4, it is obviously abnormal. We see hypochromic cells, nucleated red blood cells, little misshapen things, large flat macrocytes—every abnormality in the book. The blood sample shown in Figure 4 is from a child who had undergone splenectomy, and obviously there is a gross defect in hemoglobin production. However, the bone marrow of such patients (Figure 5) is extraordinarily active. With feeling I call this type of marrow a "university committee-type bone marrow"; in other words, as Dr. Finch* showed many years ago, there is tremendous activity but little output. The whole marrow is, in fact, crammed with red blood cell precursors expanding the total erythron, an expansion probably greater than in any other condition. Finch's data and some more recent data show that these children may have an erythron expansion that is approximately 30 times normal, a tremendous marrow hyperplasia.

In the mid-1950's and the 1960's, we tried to develop a method for measuring the rates of alpha and beta chain production in these marrow cells. I was fortunate enough when I returned to Hopkins to work part time in the Biophysics Department. There they had afternoon tea, a very civilized activity that I thoroughly recommend to any research department because it was at tea that I met a young protein chemist, Dr. Clegg.† Dr. Clegg had never seen hemoglobin but had just completed his doctoral dissertation on a method for separating fibrinogen chains. We talked about how one goes about separating globin chains, and we then used the fibrinogen method and it worked.

We labeled reticulocytes with radioactive amino acids for a short period of time and then precipitated all of the globin. We applied the material to an ion exchange column that separated

*Clement A. Finch, MD, Professor of Medicine, University of Washington Medical School, Seattle.

†John B. Clegg, PhD, Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford University, Oxford, England.

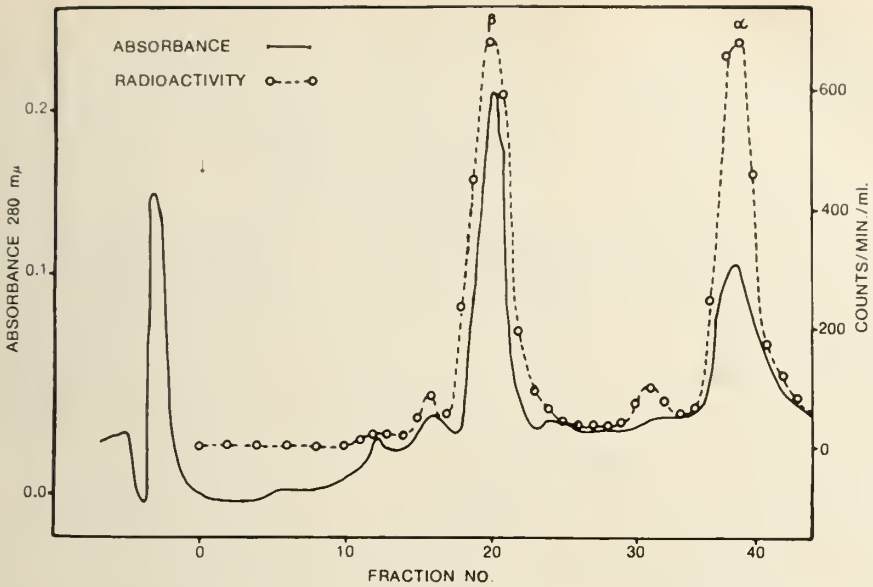

Figure 6.—Globin chain synthesis in nonthalassemic reticulocytes. Cells were incubated for 1 hour with [^{3}H] leucine and the chains were separated on CM-cellulose columns using 8 M urea/mercaptoethanol buffer, pH 6.8.

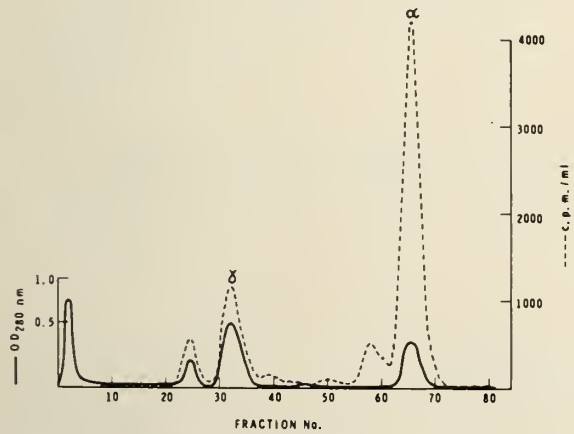

Figure 7.—Globin chain synthesis in homozygous beta°-thalassemic reticulocytes. The conditions are the same as in Figure 6.

the alpha and beta chains and determined the amount of radioactivity incorporated into the alpha and beta chains. This gave us a rough idea of the relative rates of alpha and beta chain production.[2] Figure 6 shows one of our early experiment of this type. The continuous line represents the protein emerging from the column; the first peak is the beta chain, and the second peak is the alpha chain. The continuous line shows a smaller alpha chain peak because alpha chains have different optical properties, but the amount of protein is about the same, the broken line is radioactivity. These reticulocytes were from a normal person who was synthesizing, according to the radioactivity, equal amounts of alpha and beta chains. Figure 7 shows a totally different picture for a patient with thalassemia. The dotted line, or the radioactivity, shows that the child is making no beta chains, just the gamma chains of fetal hemoglobin and alpha chains. Note the tremendous discrepancy between gamma and alpha chain production. This imbalanced globin chain synthesis is the general finding in all forms of thalassemia.

Thus if we think about the patient, the blood picture, the bone marrow and these findings, we can examine the pathophysiology of the disease, shown in Figure 8. These children cannot make beta chains; they continue to make alpha chains and make gamma chains in some of their red blood cells precursors but not in others. They have cells with excess alpha chains, which are unstable and precipitate in the bone marrow. Presumably many of these cells containing precipitated α chains never get into the peripheral blood. This is the basis for ineffective erythropoiesis; the marrow is massively hypertrophied and results in increased iron absorption. Some cells do get out of the marrow, but they have rigid inclusions in them and are thus trapped in the spleen and liver where hemolysis occurs. These children require blood transfusions, and most of them die in their second decade from iron overload owing to the increased iron absorption and repeated blood transfusions. The anemia produces tissue anoxia and hypoxia. Furthermore, fetal hemoglobin itself has a high oxygen affinity with a shifted oxygen dissociation curve so that there is a tremendous drive to erythropoietin production. This results in erythroid hyperplasia, tremendous expansion of the erythroid mass, skeletal deformities, a hyper-

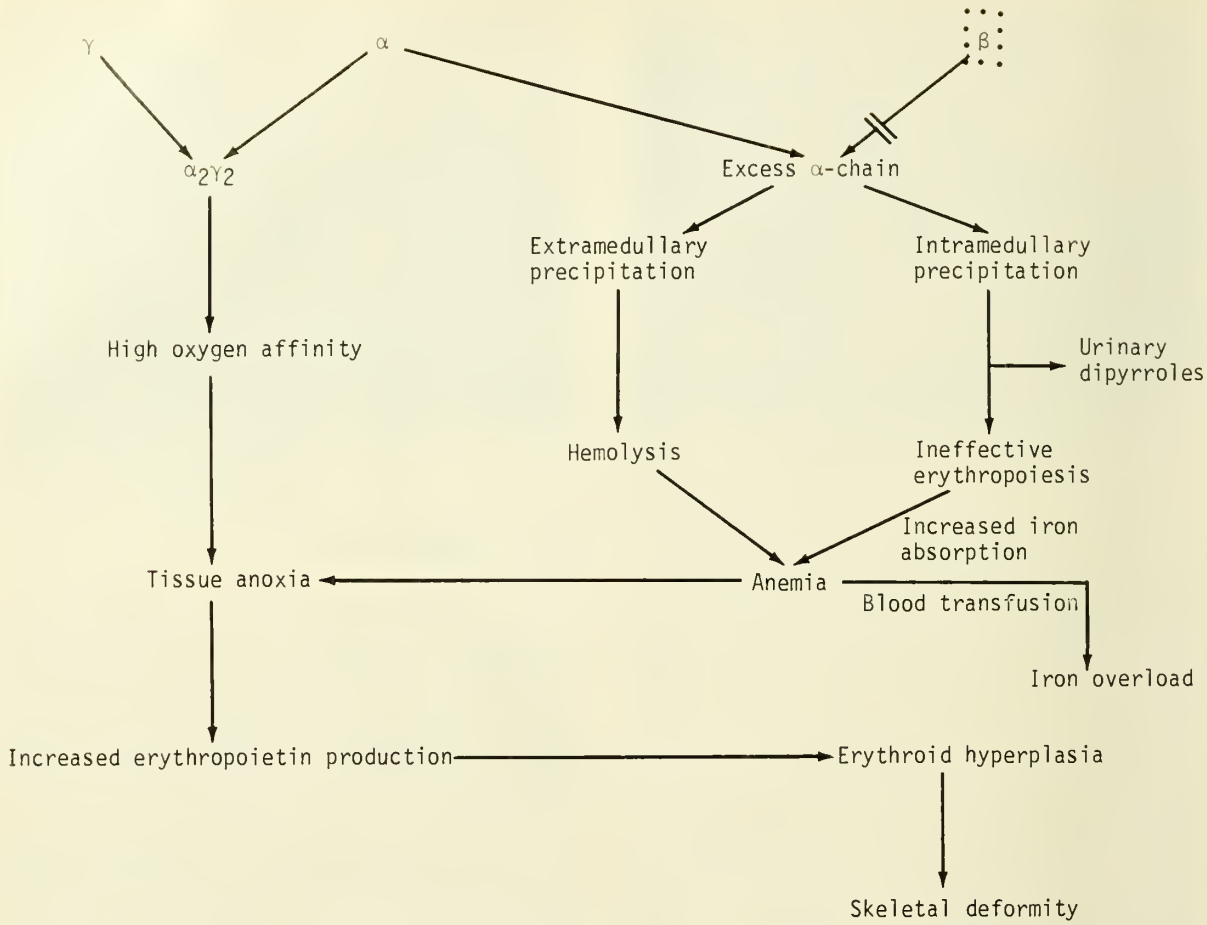

Figure 8.—Pathophysiology of beta-thalassemia.

metabolic state, hyperuricemia, wasting and other problems. It is remarkable how all of these things revert simply by adequate blood transfusion and reduction of the size of the erythroid mass in these patients. Although there are some questions about this model, basically it relates the primary genetic β chain defect to the clinical findings.

Why cannot these patients make beta chains or why cannot patients with alpha-thalassemia make alpha chains? Figure 9 reviews the basic steps in gene expression. Imagine a large red blood cell precursor with the nucleus above and the cytoplasm below. The genetic information for the globin chains is in the deoxyribonucleic acid (DNA) of the individual genes. There is good evidence that this material is first transcribed to heterogeneous nuclear ribonucleic acid (RNA), a great big molecule, and that this is then processed and its size reduced in the nucleus to the smaller definitive messenger RNA that forms the cytoplasmic template for protein synthesis. We know that in addition to the coding part, the messenger RNA contains some extra material and that it has a tail, a poly-adenylate-rich (poly A) tail. The function of the poly A tail is poorly understood at the moment. When the messenger RNA gets into the cytoplasm a series of complex steps occurs to initiate protein synthesis. New amino acids are brought on transfer RNA's into the correct position. The whole growing protein chain is held together on a kind of jig or pulley form by the ribosomes, and the whole apparatus moves along the messenger with the growing chain until it reaches a stop signal and drops off. The thalassemic defect, therefore, could be anywhere along the way.

In the mid 1960's and early 1970's, we could only work at the cytoplasmic level and ask questions about whether the processes of chain initiation, elongation and termination were normal or not. Dr. Clegg and I, and one or two groups in the United States, wasted much of the prime of our lives looking at these problems, and basically the answer was a lemon. We found that in thalassemics the processes of chain initiation and elongation are all completely normal. This suggested

to us in the late 1960's that these patients probably have a deficiency of specific globin messenger RNA but that the messenger that is there is probably functioning properly. A major breakthrough came with the ability to isolate mammalian messenger RNA, mainly through the work of people such as Dr. Lingrel.* This enabled one to assay for messenger RNA in a cell-free system. This again led to clear-cut evidence that the beta-thalassemics have a deficiency of beta chain messenger RNA and alpha-thalassemics have a deficiency of alpha chain messenger RNA. It was quite clear that we had to look into the nucleus to make any further progress in the molecular pathology of these diseases.

*Jerry B. Lingrel, PhD, Professor of Biological Chemistry, University of Cincinnati College of Medicine, Cincinnati.

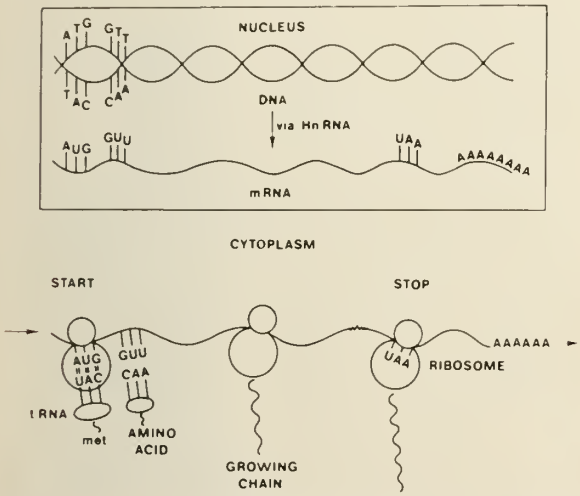

Figure 9.—Simplified scheme for protein synthesis in red blood cell precursors. DNA = deoxyribonucleic acid; RNA = ribonucleic acid; Hn = heterogeneous nuclear, M = messenger.

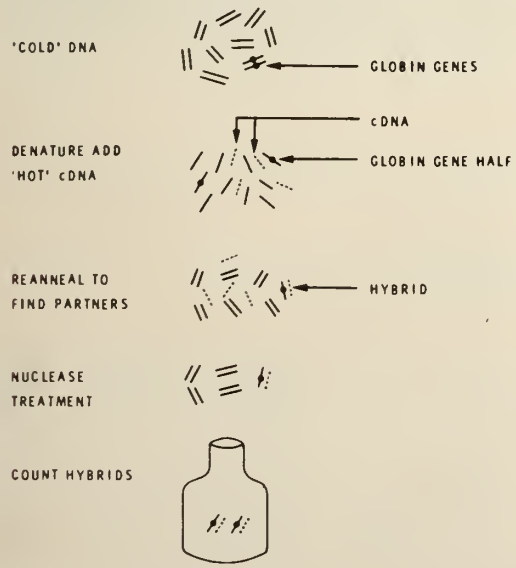

Figure 10.—Use of cDNA as a molecular probe. DNA = deoxyribonucleic acid. cDNA = complementary DNA.

The next major breakthrough came with the ability to make a DNA copy of messenger RNA. We can take specific messenger from human reticulocytes or bone marrow, mix it with a reverse transcriptase from a variety of sources and produce a partial copy of radioactively labelled DNA complementary to that material. This suggested that it might be possible to study some of these problems at the gene level rather than at the cytoplasmic level. The kind of question we can ask is shown in Figure 10. To determine whether in the genomes of these thalassemic children the genes for making alpha or beta chains are present or are deleted, we can take from one of these children some total cellular DNA, which should contain the globin genes, denature it, separate the strands and add some of our radioactive complementary DNA probe, which will bind only

Figure 11.—Infant with hemoglobin Bart's hydrops fetalis at autopsy.

to complementary DNA sequences in the DNA. We can then with one of several methods get rid of the unbound radioactive probe and count the hybrid molecules to determine whether the DNA from the patient contained any DNA sequences which could bind to our probe. This is the approach that our own group and that of Dr. Williamson* and his colleagues in Glasgow decided to use in thalassemia. Of course, independently Dr. Kan was thinking exactly along the same lines in this country.

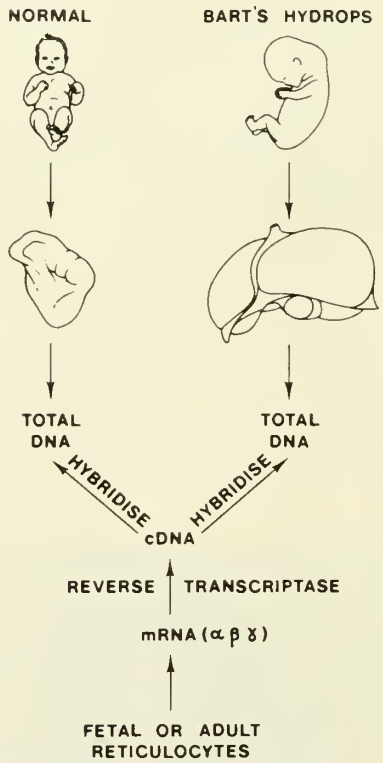

Figure 12.—Experimental design of alpha chain gene probe study. DNA=deoxyribonucleic acid; RNA=ribonucleic acid (From Weatherall DJ: Molecular basis for some disorders of haemoglobin synthesis—II. Brit Med J 4:516-519, 1974. Reprinted with permission from the publisher).

We decided first to do the obvious experiment.[3] Hydrops fetalis, which is the most severe form of thalassemia, is shown in Figure 11. Dr. Lie-Injo,† who is in the audience today, first described this syndrome in Malaya and Indonesia. This form results from homozygous alpha-thalassemia-1. These fetuses make no hemoglobin A or F, and synthetic studies carried out a few years ago showed that they make no alpha chains and no alpha chain messenger RNA. So the obvious first question was whether these fetuses have any alpha chain genes. The kind of experiment that we did and that Dr. Kan did at the same time is shown in Figure 12. From fetal or adult reticulocytes, we isolated messenger RNA by the methods previously suggested and used reverse transcriptase to make a DNA copy. With more sophisticated techniques, we try to make much cleaner copies of alpha, beta or gamma DNA and use these probes to determine whether or not these patients have copies of specific genes in their genomes. We obtain tissue from a patient with hydrops fetalis and from normal subjects and measure the rate of or the degree of hybridization of these probes with the DNA from these tissues. Figure 13

*Robert Williamson, MD, Beatson Institute for Cancer Research, Glasgow, Scotland.

†Luan E. Lie-Injo, MD, PhD, Research Hematologist, Department of International Health and Hooper Foundation, University of California, San Francisco.

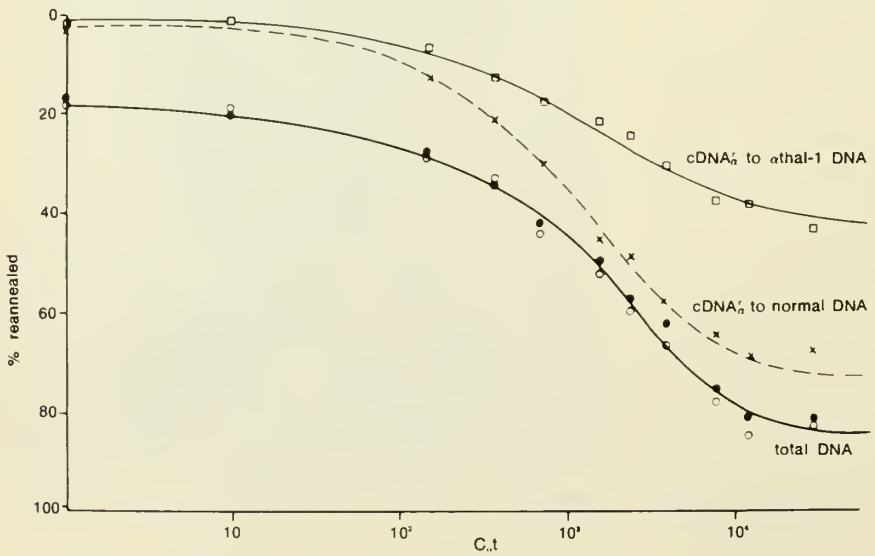

Figure 13.—Rate of hybridization of the cDNA to cellular DNA from normal and hydrops babies. (From Ottolenghi S, et al: Gene deletion as the cause of α thalassemia. Nature 251: 389-392, 1974. Reprinted with permission from the authors and publisher.)

shows the type of result that we and Dr. Kan observe when we hybridize the purified alpha chain DNA probe to the total DNA from a normal subject or from a patient with thalassemia. Normal alpha chain probe reanneals to the DNA from normal persons at the rate one would expect, whereas the alpha chain DNA probe hardly hybridizes at all to DNA from the patients with alpha-thalassemia. The probe used in the depicted experiment was a pure alpha probe because there is a little hybridization. Dr. Kan, who has really done the most exciting work in this area, and in the United States, went on to show that the hydrops fetuses have no alpha chain genes. Since we know there are two alpha chain genes, this suggested that the alpha-1 defect was in fact owing to a deletion of both genes. He further showed that the alpha-2 genetic defect is probably due to a loss of only one of these genes.

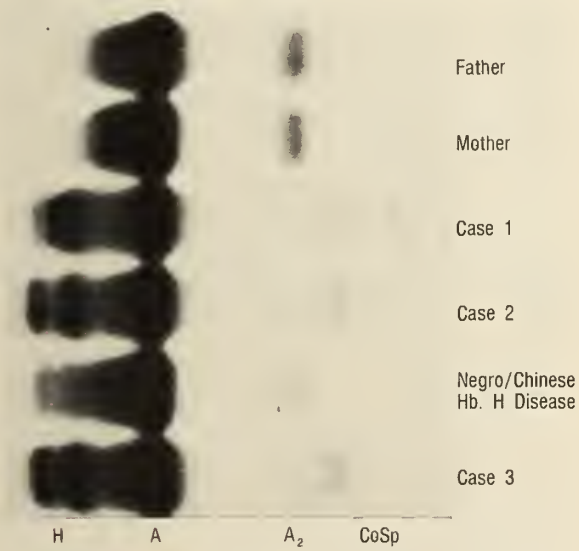

Figure 14.—Hemoglobin Constant Spring family; hemoglobin analysis. Hemoglobin Constant Spring shown as cathodal bands. (Starch gel electrophoresis, pH 8.5, benzidine stain. For details see Milner PF, et al: Haemoglobin-H disease due to a unique haemoglobin variant with an elongated α-chain. Lancet 1:729-732, 1971.)

```
            141
.......Tyr.Arg.GLN.ALA.GLY.ALA.SER.VAL.ALA.
....———α———

            149            ——CS 3—
            VAL.PRO.PRO.ALA.ARG.TRP.ALA.SER.

            157
            GLN.ARG.ALA.LEU.LEU.PRO.SER.LEU.

            165        ——CS 2—        172
            HIS.ARG.PRO.PHE.LEU.VAL.PHE.GLU
```

Figure 15.—Structure of hemoglobin Constant Spring. Tyr=tyrosine; Arg=arginine; GLN=glutamine; ALA=alanine; GLY=glycine; SER=serine; VAL=valine; PHE=phenylalanine; PRO=proline; GLU=glutamic acid; CS=Constant Spring.

To complete the alpha thalassemia story, we must go back again for a year or two. Figure 14 shows electrophoretic patterns of hemoglobin from a family sent to us by Dr. Milner* from Constant Spring, a suburb of Jamaica. The hemoglobin was placed in a slot in starch and electrical current applied. At the top the parent's patterns reveal hemoglobin A and hemoglobin A_2, the minor band. The three siblings, cases 1, 2 and 3, had, in addition to hemoglobins A, a hemoglobin H and the slow components (bands on far right, CoSp) that Milner did not recognize immediately. They turned out to be both components of the same hemoglobin. We called this hemoglobin Constant Spring for the suburb from which this family came.

When we learned how to isolate these trace bands of material and to examine their structure, they turned out to be rather unusual. Figure 15 shows that normal alpha chains have 141 amino acids, whereas the Constant Spring variants have in addition to the normal 141 amino acids of α-chains, an extra 30-odd residues stuck on at the C-terminal end, the distal end of the chain. This material is synthesized at a reduced rate and thereby produces the clinical picture of thalassemia. Inheritance of this gene from one parent and the alpha thalassemia-1 gene from the other would result in hemoglobin H disease. The question was, Why did somebody make an elongated globin chain and why did this produce the clinical picture of thalassemia? It did not make any sense; it was like no protein on earth, and even the computer could not make any sense of it.

We made a rather, what we thought, naive suggestion back in the early 1970's, that this globin chain is the result of a simple gene mutation in which there is a single-base change in the codon that normally signals stop to protein synthesis. The UAA codon is the normal stop word, certainly in bacteria and probably in man. Let us say that we have changed the U to a C. Now instead of saying stop, CAA is the code word for glutamine; instead of the protein chain ending at 141, the machinery would put in glutamine at

*Paul M. Milner, MD, Medical College of Georgia, Augusta.

142, and then it would continue synthesizing on the rest of the messenger RNA until it reached another stop word. The chain would end up elongated with glutamine at position 142 and a lot of extra residues. The elongated α chain is made quite slowly for unknown reasons. This elongated message that is read beyond the normal stop word is synthesized only in early red blood cell precursors, and the synthesis appears to decline very early during erythroid maturation. Thus one ends up with fewer alpha chains and a condition similar to alpha thalassemia. We received the usual kind of knowing looks from our molecular biology friends in Cambridge about this model and the usual remarks about physicians doing better to look after patients than get involved in this kind of thing that they do not understand. In fact, it worked out rather nicely, because a little bit later something else happened.

Figure 16, line 2, shows the normal alpha chain ending in arginine at position 141; we found that Constant Spring went on from arginine to glutamine to the great long tail. The next key in the argument came with the discovery of hemoglobin Wayne in this country. Again, this was an elongated hemoglobin variant, but in this case, it was not quite like Constant Spring; it was normal up to residue 138, and then suddenly changed completely and ended in arginine at 146. The nice thing about this was that it has been known for years that in microorganisms one can have a type of mutation called a "frame shift." In the genetic code if a nucleotide is lost, everything gets moved along one so that the protein synthesizing machinery suddenly begins to read out of phase sequence and thus produces an altered product. If we imagine that hemoglobin Wayne has arisen by a loss of the U at position shown by the bracket in Figure 16 and everything has shifted along one, then the new sequence for hemoglobin Wayne is produced and UAG is produced at position 147, which is the other terminating codon in microbial genetics. If we do a little bit of juggling around and stick the base back in as it were, we not only can produce the Wayne sequence but also can actually produce the first part of the Constant Spring sequence. This was too much of a coincidence, and then we thought that if we can have one mutant resulting from a substitution of the chain-terminating codon, UAA to CAA at position 142, as in Constant Spring, there must be other mutants, since there could be other substitutions at this position. Sure enough, blood from a thalassemic family on one of the Aegean islands turned up with a Constant Spring-like hemoglobin and it looked slightly different; it had a different charge, and it turned out to have lysine, not glutamine, at position 142. The rest of the tail was exactly the same. Thus there is a whole family of these chain termination mutation hemoglobins. In fact recently, structural studies have shown that this area of extra messenger RNA does in fact exist and have shown there to be nucleotide sequences that are similar to the sequences required for the tail of Constant Spring.

If we look at the chain termination mutants, we can summarize them as shown in Figure 17. At the terminating codon, if UAA changes to CAA, we get Constant Spring; if it changes to AAA, it codes for lysine and we get hemoglobin Icaria. The next thing to turn up was UCA, serine and Koya Dora. We predicted three more and almost before we could make the illustration, Dr. Bradley* of this university published an abstract on hemoglobin Seal Rock. This is the same type of mutation but with apparently glutamic acid in position 142. Maybe the others are already

*Thomas B. Bradley, Jr, MD, Professor of Medicine, University of California, San Francisco, and Member of the Staff, Medical Service, Veterans Administration Hospital, San Francisco.

Figure 16—Structures of hemoglobins Constant Spring, Icaria, and Wayne showing base replacements. Thr=threonine; Lys=lysine; Asn=asparagine; see Figure 15 for remainder of abbreviations. (From Clegg JB, et al: Haemoglobin Icaria, a new chain-termination mutant which causes alpha thalassaemia. Nature 251: 245-247, 1974. Reprinted with permission from the authors and publisher.)

known, but there are only three left and one of them will mutate to another terminating codon so it will not do any harm. We have just two to find.

It may sound esoteric but in fact, if one looks at the gene frequency of these abnormalities, it becomes less esoteric. Dr. Lie-Injo found hemoglobin Constant Spring quite independently in Malaya. In the early 1970's it was found independently in Greece and Thailand, and it is now known that two to three percent of the population of Thailand are carriers for hemoglobin Constant Spring. So it is not all that rare and it certainly occurs frequently on the Malay peninsula and in other populations.

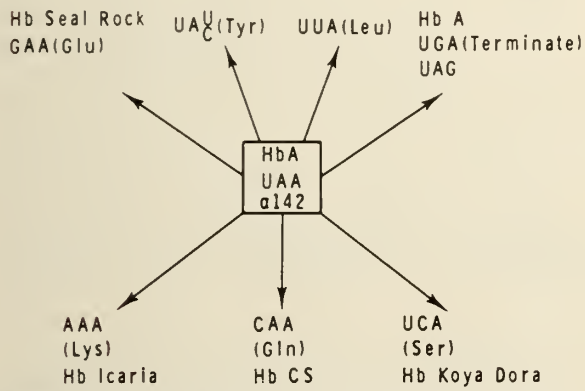

Figure 17.—Summary of chain termination mutants. Hb = hemoglobin; see Figures 15 and 16 for remainder of abbreviations.

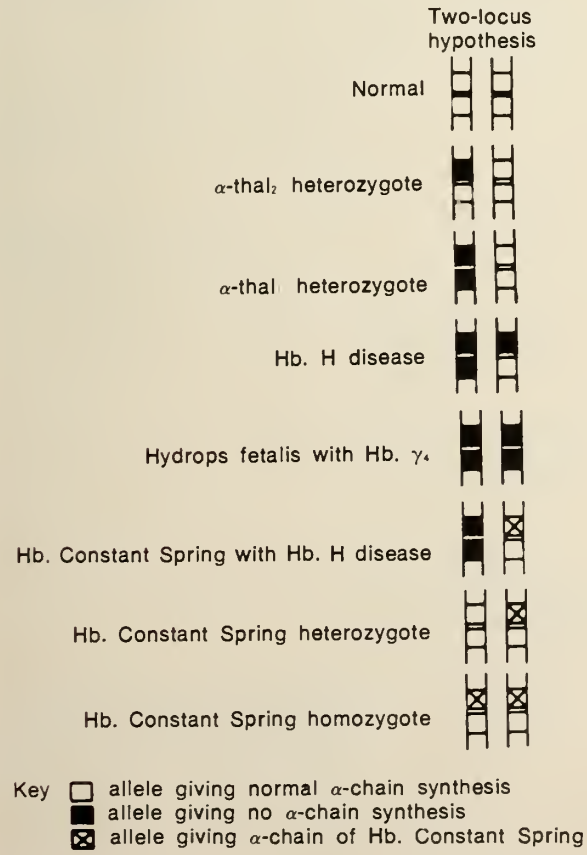

Figure 18.—Schematic representation of data in Table 3. Hb = hemoglobin.

Table 3 summarizes the molecular basis of the common alpha thalassemias. In alpha-thal-1, the bad mutation gene, we are convinced that both alpha chain genes are probably deleted. In alpha-thal-2, the not so bad mutation, Dr. Kan showed beautifully that one of these pairs of genes is deleted. Finally, there are the chain termination mutants, for which Constant Spring is the prototype, in which alpha chain synthesis is reduced, resulting in a clinical picture of alpha-thalassemia. Figure 18 depicts the two human chromosomes: the normal ones have two alpha chain genes on each chromosomes; heterozygote for the mild alpha thalassemia has lost one of the loci and only three of the four loci are therefore functioning; and the heterozygote for the severe alpha-thalassemia has lost both loci so only two are functioning. Heterozygotes for alpha-thal-1 or α-thal-2 are not sick. The double heterozygote with the severe allele from one parent and the not so severe allele from the other parent has one functioning alpha locus and hemoglobin H disease. The homozygote with four bad alleles from both parents dies *in utero;* this is a frequent cause of fetal deaths in Southeast Asia. The Thais now are able to give us data on more than 500 patients with hemoglobin H disease, which is a major problem in that country. Some of the patients are very sick and some of them are not so sick. The incidence of hemoglobin H disease is frequent in the Orient and less frequent in the Mediterranean region. The Constant Spring heterozygote with the severe thalassemia-1 gene from one parent and the Constant Spring allele from the other has the same type of hemoglobin H disease; for practical purposes, the Constant Spring mutation just stops one locus from functioning. Dr. Lie-Injo discovered the first homozygote for Constant Spring. The patient had a very mild thalassemia-like disorder because two of the alpha chain loci were functioning. These which we have discussed are the common forms of alpha-thalassemia, but there are alpha-thalassemias in other populations that we do not yet understand.

To check the human model shown in Figure 18 we were interested in obtaining a model of

alpha-thalassemia in an animal system. Horses have two alpha chain genes that can be separated by a structural change in one residue. Dr. Clegg found a race horse in Norway that appeared to be missing one of these pairs of genes. However, the owner did not want to breed it, and when he heard it was interesting, he wanted to breed it even less. We got in touch with the President of the Royal College of Physicians who is a geneticist and told him about the problem. He (and this is how things work in Europe; you cannot do things like this in the United States) happened to be having dinner with the Queen Mother and mentioned horses and this problem, and she said, "I will get in touch with my friend the King of Norway." About two months later, we received a letter from the race horse owner in Norway saying that he was very keen to breed the horse, but that he would require stud fees of 4,000 pounds sterling. The Norwegian Veterinarian College raised half of it, and we raised the other half. If you ever try to raise medical research

TABLE 3.—*Molecular Basis of Alpha-Thalassemia*

Thalassemia	*Phenotype*	*Current State of Knowledge of Molecular Pathology*
α-thal-1	No α chain synthesis	Both α genes deleted
α-thal-2	Reduced rate of α chain synthesis	One α gene deleted
Hemoglobin Constant Spring etc.	Reduced rate of α chain synthesis due to negligible production of α Constant Spring	Chain termination mutation, ? unstable α mRNA

mRNA = messenger ribonucleic acid

TABLE 4.—*The Beta-Thalassemias. Current Understanding of the Molecular Basis*

Thalassemia	*Phenotype*	*Current State of Knowledge of Molecular Pathology*
β thal⁺	Severe reduction in β chain synthesis	Reduced synthesis of β mRNA
β thal⁺ (Negro)	Mild reduction in β chain synthesis	No data
β thal⁺ (High F)	Mild reduction in β chain synthesis	No data
β-thal⁰	No β chain synthesis	No β mRNA present, β gene present
β-thal⁰ (Ferrara)	No β chain synthesis normally but inducible	? β mRNA may be present
δβ-thal⁰	No δ or β chain synthesis	No δ or β mRNA present, δ and β genes deleted
δβ thal⁺	Reduced rate of δ and β chain synthesis	No data
δβ (Lepore)	Composite δβ chain synthesized in reduced amounts	δβ fusion gene—mRNA may be unstable

mRNA = messenger ribonucleic acid

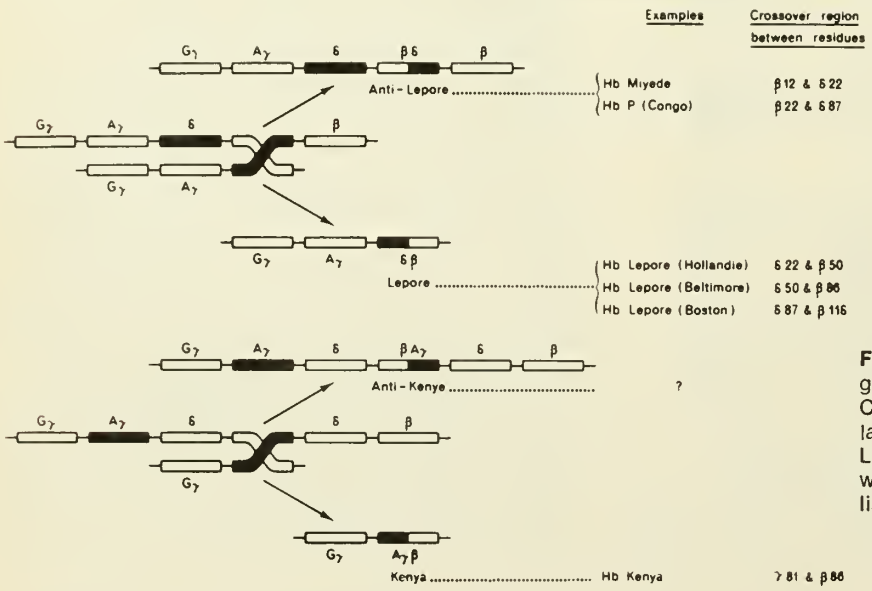

Figure 19.—The crossover hemoglobins. Hb = hemoglobin. (From Clegg JB, Weatherall DJ: β⁰thalassemia—time for a reappraisal? Lancet 2:133-134, 1974. Reprinted with permission from the publisher.)

TABLE 5.—*Summary*

Molecular Defects
- Point mutation
- Deletions of one or more bases
- Frame shifts
- Chain-termination mutations
- Whole-gene deletions
- Abnormal crossing-over
- ? others

Therapeutic Possibilities
- Antenatal diagnosis
- Single gene replacement
- Fetal hemoglobin activation
- Selective globin-chain inhibition

money for stud fees, let me know, as it is not easy. Anyway, the horse has spent a very pleasant summer, we gather, and we are hoping that we will find at least an alpha-thalassemia type 2 mutation in the animal model.

The beta-thalassemia situation is quite different; it is much more complicated, and not well understood. Table 4 summarizes some of the disorders. The severe beta-thalassemias have reduced production of messenger RNA. Our group and Dr. Kan's have found that the DNA from patients with beta^0-thalassemia contain beta genes even though the patients have no gene products. Some seem to have an absence of beta messenger RNA and some seem to have some nonfunctional beta messenger RNA. Certainly, this is the case in the type of beta^0-thalassemia from Ferrara, Italy. Our preliminary data on delta-beta-thalassemia suggest that the genes are deleted. There is considerable heterogeneity in these forms, which presents a real problem in sorting out the molecular basis for the reduced rate of messenger RNA synthesis in beta$^+$-thalassemia.

The last type of thalassemia is Lepore hemoglobin (Table 4). Lepore brings us to our final molecular mechanism. Some of the thalassemias result from abnormal chromosomal crossing-over. If two chromosomes are side by side with homologous loci, such as the beta and delta loci, a genetic accident may occur during crossing-over as shown in Figure 19. The order of genes on the chromosome is the G gamma and A gamma loci followed by the delta and beta loci. Unequal crossing-over results in a composite delta-beta gene, which makes the delta-beta chain. Dr. Gerald* first described this hemoglobin in the late 1950's and called it Lepore after the family name. There are three types now (Lepore Hollandia, Baltimore and Boston), all owing to different point of gene crossover. Of course, on the other chromosome you have an anti-Lepore gene, a beta-delta gene. The delta-beta chain is interesting because the corresponding messenger RNA is unstable as is the messenger RNA for the normal delta chain of human hemoglobin; they are only made for a short period during erythroid maturation. We thought that messenger instability might be a property of all these unequal crossover hemoglobins but found that it is not. We studied another extraordinary crossover in a kind of half-fetal and half-adult hemoglobin, hemoglobin Kenya, in which the beta and gamma chains have crossed-over. We found that the material is synthesized normally throughout erythroid maturation. Thus the delta chain genes seem to have areas that are involved in stability of messenger RNA. These crossover variants with bits of delta chain sequence have unstable messengers, early cessation of globin chain synthesis and globin chain imbalance, and result in the clinical picture of thalassemia. This group again is separate altogether and provides another molecular basis for thalassemia.

Now, I would like to summarize and try to put this information into perspective as a clinician rather than a laboratory investigator (Table 5). In the hemoglobinopathies and thalassemia we have almost everything that the microbial geneticists would have predicted: simple mutations, deletions, frame shifts, chain termination mutations, loss of whole genes and abnormal crossing-over, all producing the clinical features of the thalassemic disorder. What can we do with this vast amount of information? Well, Dr. Kan and Dr. Nathan's† group showed that if we can sample fetal blood early in pregnancy, we can make an antenatal diagnosis of sickle cell anemia and beta-thalassemia. The techniques are difficult, sophisticated and hard to imagine being used on a broad scale in the developing countries—although it may be possible. It is a technical problem anyway. Furthermore, although it is a long way off, the techniques that are being used to isolate the globin genes and to grow them in plasmids, and so on, to produce large amounts of DNA will at least allow us to look at the structure of the DNA and possibly work out some of the molecular defects in beta$^+$-thalassemia. It is a

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†David G. Nathan, MD, Professor of Pediatrics, Harvard Medical School, Boston.

proliferative disease and if we had a selective method of reducing globin chain synthesis, we might be able to do something about the proliferative aspects, but again this seems unlikely. Finally, everything tells us that if we were able to reactivate gamma chain synthesis in these cells, the beta thalassemia problem would no longer exist. Many years ago I read a book review in an American medical journal. The author reviewed a famous English textbook of medicine, which I will not mention, and obviously did not like it. He made a memorable closing in the review by stating that when he opened the book, he noticed on the first page that the senior author was Physician to Her Majesty the Queen and when he closed the book, he felt his final thoughts could only be, God save the Queen! I have to tell you that she is well and alive 20 years later despite her physicians. I tell you this just to point out that unlikely things happen in clinical medicine, and therefore perhaps we may hope that within five to ten years we may be able to have a Paul Aggeler Lecture on developmental aspects of hemoglobin production and the therapeutic use of the change from fetal to adult hemoglobin production in these disorders. As far as I can see, the gene manipulation type of approach is the only feasible approach.

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Important Advances in Clinical Medicine

Epitomes of Progress—Radiology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Radiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Radiology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Radiology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Gray Scale Ultrasonography

ULTRASONIC CROSS-SECTIONAL TOMOGRAPHY using pulsed-echo techniques has gained wide clinical acceptance as a new diagnostic tool. The technique has been applied successfully in the differential diagnosis of a number of pathological processes involving many organ systems. Tissue differentiation by ultrasound is based on acoustic impedance discontinuity, which in turn is related predominately to differences in soft tissue elasticity and density. The first instrumentation developed for two dimensional ultrasonic imaging used storage oscilloscopes to record the reflected echoes. The major disadvantage of this type of signal recording was the limited ability to display the dynamic range of the returning echoes, that is, the amplitude information.

Recently, systems have been developed that are capable of preserving quantitatively the amplitude information. They have been termed "gray scale." At first, conventional nonstorage oscilloscopes were used for display and the image was built-up on a film by continuous exposure during the scanning period. Commercial manufacturers in this country have adopted a different type of recording process to preserve amplitude information. The systems make use of a television scan-converter as the temporary recording target instead of a storage oscilloscope. Magnitude information is read from the scan-converter, converted to a shade of gray and relayed to a television monitor for the final display.

With the newer signal processing, reports are already appearing in the literature confirming the anticipated improved resolution and soft tissue differentiation. Cold thyroid nodules on nuclear scans can not only be characterized as to their cyst-solid nature, but preliminary reports suggest benign versus malignant solid processes can also be differentiated. A similar type of experience has been reported with palpable breast nodules. The accuracy of placental localization is approaching 100 percent with the newer techniques. Gross congenital anomalies are more readily discovered *in utero* and hydrocephalus more accurately assessed in the neonate and early infant. A normal pancreas, which previously was rarely visualized using the older instrumentation and has always been a difficult diagnostic area with

conventional radiography, can now almost routinely be seen in whole or in part. The evaluation of liver disease has been remarkably improved with better visualization of both primary and metastatic liver abnormalities as well as improved differentiation between surgical and medical jaundice.

W. F. SAMPLE, MD

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Arteriographic Documentation of Coronary Arterial Spasm in Prinzmetal's Angina

PRINZMETAL'S VARIANT ANGINA is a syndrome characterized by angina occurring at rest in association with electrocardiographic ST segment elevation. While the presence of high grade lesions in the proximal portion of a major coronary artery can be shown in some patients with variant angina, the coronary arteries in others may be normal at the time of coronary arteriography. Moreover, infrequently the coronary arteriogram has been entirely normal in patients with previously documented myocardial infarction. Whereas spasm of the coronary artery has been theorized as the pathogenetic mechanism in these patients, isolated case reports in recent years have actually noted significant spasm of a major coronary artery in patients with Prinzmetal's angina.

Coronary arteriography in 17 consecutive patients with Prinzmetal angina at the University of California, San Diego, showed there to be high grade fixed obstructive lesions of the coronary arteries in nine patients and normal or insignificant lesions in the other eight patients. In three of the latter patients, there developed spontaneous spasm of the mid-right coronary (one patient), main circumflex coronary (one patient) or obtuse marginal branch artery (one patient) during the arteriographic procedure. In each instance the spasm was sufficiently severe to produce total occlusion of the involved vessel. Angina and ST segment elevation appeared concomitant with the coronary arterial spasm. Coronary arterial spasm, angina and ST segment changes were abolished by sublingual nitroglycerin administration.

Provocative pharmacoangiography, which consisted of the intravenous administration of ergonovine maleate, caused localized spasm of the right coronary artery in two other patients with Prinzmetal's angina. Again, angina and ST segment elevations occurred with the spasm and were instantaneously abolished by administration of nitroglycerin. Other investigators report a similar experience with the drug in this syndrome. Provocative pharmacoangiography in ten patients with arteriographically normal coronary arteries and chest pain, which was not characteristic of Prinzmetal's angina, did not cause coronary arterial spasm.

Therefore, coronary arterial spasm is the responsible pathogenetic mechanism for myocardial ischemia in many patients with Prinzmetal's angina and this phenomenon can be shown during coronary arteriography.

CHARLES B. HIGGINS, MD

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Real Time Ultrasonography of the Abdomen and Pelvis

RECENT ADVANCES in technology now permit a diagnostician to examine the abdomen and pelvis in any patient and view a two-dimensional cross section in real time. In other words, there is simple instrumentation available that will allow a physician to observe a type of fluoroscopic tomogram, the location of which is easily selected by a hand-held array of transducers.

Vascular structures such as the abdominal aorta and the inferior vena cava are readily

visualized and may be observed during various physiological maneuvers. It has been our experience that disease entities such as right heart failure, tricuspid insufficiency and constrictive pericarditis produce a continuous dilatation of the inferior vena cava that does not vary with a phase of respiration. Differentiating between abdominal aortic aneurysms and periaortic masses is quite simple and requires less than five minutes.

Other vascular structures within the abdomen —such as the portal venous system, superior mesenteric artery, superior mesenteric vein and splenic artery—also seem to be reliably shown using the technique in more than 75 percent of the patients examined.

The noninvasive, nonionizing nature of the ultrasound technique has obvious applications in pregnancy. Not only can a diagnostician speedily determine the number and positions of fetuses present, but accurately describe and locate the placenta for possible amniocentesis. This diagnostic information obviates the need for ionizing radiation in the case of suspected multiple gestations, as well as a blind insertion of the amniocentesis needle. Locating the fetal head and determining the biparietal diameter requires only minutes. The ease of use of the real time scanning unit also overcomes the traditional problems previously encountered when a fetus changed the orientation of its head. The real time unit allows for rapid reorientation of the transducer array which facilitates gestational age estimation, regardless of fetal movements. Placental characteristics such as cystic spaces, thickness, location and pulsations are easily visible. It is also possible to observe distention of the fetal bladder with subsequent emptying, fetal heart structures and respiratory-like motions of the fetal thorax.

Many more applications of this new diagnostic modality are being made every day with obvious benefit to patients.

ROBERT L. WILSON, MD
MICHAEL S. SHAUB, MD

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The Usefulness of Ultrasonography in Postoperative Patients

PATIENTS IN WHOM abdominal operations have recently been carried out are frequently difficult to examine both clinically and radiographically due to the presence of incisions, bandages and drains. Often the source of complications occurring in these patients, such as abscesses, is frustratingly elusive. Findings on routine abdominal radiographs including plain films, intravenous urograms and barium studies often are not conclusive until a mass is large enough to distort or displace an organ or until an extraluminal gas collection is noted.

B-mode ultrasound is frequently helpful in discovering the source of many postoperative complications. This technique visualizes the area of pathology directly instead of inferring its presence by noting abnormalities in adjacent structures. The examination is nontraumatic, and can be done at a patient's bedside if necessary. Wound contamination can be avoided if the examination is carefully and properly carried out.

Intraabdominal abscesses can be detected when they are larger than 3 cm. The appearance of an abscess is variable due to the presence of differing amounts of debris within them, but usually they are seen as irregular sonolucent areas. Special attention should be given to dependent regions such as the pelvis and subphrenic space, as well as those areas in the immediate vicinity of incisions and drains. The pelvic area should be scanned when the bladder is full to ensure deep penetration of sound. The subphrenic area can be particularly difficult to examine. When evaluating this area it has proved most advantageous to place the patient in a supine position and make the scans in a longitudinal fashion. Posterior longitudinal scans also should be done while the patient is sitting in an erect position (if possible). Decreased or absent diaphragmatic mobility also should be noted. Superficial wound abscesses are delineated by scanning the area circumscribing an incision. These abscesses frequently encompass much larger areas than are clinically appreciated.

In patients with suspected retroperitoneal postoperative complications, it is imperative that the scan be done from a posterior position in order to deliver enough sound to the area in question. If a patient cannot lie in a prone position, an adequate scan can nonetheless be obtained by

carrying out the examination with the patient in either a decubitus or sitting position.

Postoperative patients in whom acute renal insufficiency develops may also be examined ultrasonically. If there is an obstructive uropathy, the presence and severity of hydronephrosis can be assessed. In addition, the appearance of echoes within the bladder should raise a suspicion of blood clots within that organ.

The limitations of ultrasound are few and are well recognized. Excessive bowel gas or barium within the bowel prevents an adequate examination. Occasionally fluid within bowel loops simulates an abscess. It is therefore important to correlate the ultrasonic findings with those noted on a recent abdominal radiograph.

FAYE C. LAING, MD

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Transcatheter Embolization

THE TECHNIQUE of purposeful selective arterial embolization, which has been applied to a variety of clinical situations, is a simple extension of the standard angiographic examination. A variety of substances have been employed as the embolus (such as autologous clotted blood or tissue, gelfoam particles, and various pellets and metallic foreign bodies), which is injected via the selectively placed angiographic catheter under close fluoroscopic control. This technique has been used to control bleeding, usually when nonresponsive to infusion of vasoconstrictors (for example, in trauma or neoplasms), and to infarct neoplasms to facilitate surgical removal or as a palliative measure.

RONALD A. CASTELLINO, MD

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Diffuse Idiopathic Skeletal Hyperostosis (DISH)

IN 1950 Forestier and Rotes-Querol described a peculiar pattern of axial new bone formation characterized by flowing ossification along the anterior aspect of the vertebral column which they termed ankylosing hyperostosis of the spine. This disorder was recognized most frequently in elderly men and associated with mild clinical findings.

A recent clinical and radiographic investigation of extraspinal manifestations in 21 consecutive patients with typical changes of the vertebral column showed there to be a high incidence of associated hyperostosis at sites of ligament attachment including the pelvis, calcaneus, ulnar olecranon and patella—and suggested that diffuse idiopathic skeletal hyperostosis (DISH) was a

Figure 1.—Radiographic film showing hyperostosis of the thoracic spine. Note the anterior linear bone formation (arrowhead) with subjacent radiolucency (lu) and radiolucent disk extensions (d). The height of the disk spaces is relatively preserved.

more appropriate term for this ossifying diathesis. Additional extraspinal radiographic abnormalities included para-articular osteophytes and ligament and tendon calcification and ossification. Although pain and decreased range of motion in the axial skeleton were the dominant clinical features, peripheral musculoskeletal complaints were occasionally the initial manifestation of the disorder and included recurrent tendinitis and restricted joint motion. The latter required surgical removal of osteophytes in several patients. The most distinctive radiographic abnormality in DISH is linear new bone formation along the anterolateral aspect of the thoracic spine (see Figure 1) with pointed bony excrescences at the superior and inferior vertebral margins, particularly in the cervical and lumbar spine.

Our radiographic and pathologic evaluation of the spines in 215 cadavers showed an incidence of DISH in 12 percent, using criteria for diagnosis that required flowing ossification of at least four contiguous vertebral bodies. Pathologic features included regional calcification and ossification of the anterior longitudinal ligament, paraspinal connective tissue and anulus fibrosis, and degenerative changes in the peripheral portion of the anulus with periosteal new bone formation on the anterior surface of the vertebral bodies.

These radiographic and pathologic alterations differ from those occurring in other disorders of the vertebral column. *Ankylosing spondylitis* predominantly affects young adults and is associated with sacroiliac and apophyseal joint sclerosis and bony ankylosis. In DISH these articulations are relatively normal. In addition the thin, bony bridges or syndesmophytes extending between the vertebral bodies in ankylosing spondylitis differ from bulky excrescences which characterize DISH. *Degenerative disk disease,* frequently occurring in elderly patients, is caused by fragmentation of the central portion of the intervertebral disk and the nucleus pulposus, and is associated with disk space narrowing. In DISH the height of the intervertebral disk spaces is usually maintained. The latter disorder most resembles *spondylosis deformans* (spinal osteophytosis) but the degree of new bone formation is excessive.

DISH may not represent a disease per se but rather extensive ossification resulting from an exaggerated response of the body in some patients to stimuli that produce only modest new bone formation in others. These patients appear to be "bone formers" which may account for the unusual tendency for hyperostosis at axial and extra-axial sites of ligament stress to develop. No definite relationship with other osteophyte-producing diseases such as acromegaly and fluorosis has as yet been established.

DONALD RESNICK, MD

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Balloon Occlusion

A New Interventional Neurovascular Procedure

A NEW TECHNIQUE is available that allows neuroradiologists to assist in the therapeutic management of certain angiomas and fistulas involving vessels going into the brain or spinal cord. By selective intra-arterial placement of small balloons, it is possible to temporarily or permanently occlude flow. The balloons are attached to catheters and fluoroscopically guided into the desired vessel.

Balloon occlusion is indicated for lesions that are surgically inaccessible or as a presurgical maneuver to determine possible ischemic damage to vital structures. In the latter instance, temporary balloon occlusion allows for neurological evaluation of an awake patient before permanent ligation.

A small Fogarty balloon catheter is percutaneously introduced into a regional artery through a larger catheter or sheath. The balloon remains collapsed until the arterial feeder is selected and then it is inflated temporarily or until a clot forms. The balloon is then deflated and the catheter removed.

Alternatively, the Fogarty balloon catheter is surgically placed into an artery and inflated, and then flow directed to the fistulous orifice. The catheter remains permanently in place after its proximal end is sealed and sutured into the surrounding tissues.

These techniques are used successfully to obliterate carotid-cavernous and vertebro-jugular

fistulas without radical surgical procedures. Arteriovenous malformations of the spinal cord can be similarly occluded if fed by a singcl vessel.

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Lymph Node Metastasis in "Apparently" Localized Prostate Cancer

AS IS TRUE in most tumors, the therapeutic approach to prostatic carcinoma is largely governed by the determination of the anatomic extent of disease. Recently, increasing attention has been focused on the importance of lymph node metastasis in this disease, which traditionally has been felt to involve the bones early and the lymph nodes only as a late manifestation. Lymphography is used to detect lymph node metastasis in patients with prostatic cancer, with the overall incidence of positive studies ranging up to two thirds of all cases, depending on thc type of patients studied (that is, the stage of the disease and whether there had been earlier treatment) and probably also on varying lymphographic criteria. Early results are of interest from a continuing study (Bagshaw and co-workers) of unselected, previously untreated patients with "apparently" localized prostatic carcinoma (that is, no evidence of metastasis by findings from standard clinical, laboratory, nuclear medicine and radiographic studies excluding lymphography). In about a third of these patients with "apparently" localized disease there was histologically documented lymph node metastasis. In such patients lymphography has an approximate 80 percent accuracy, with most errors occurring as false-negative findings.

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EDITORIALS

A BICENTENNIAL EDITORIAL

On the Governance of Health Care

HEALTH CARE may well be the largest industry in the nation, and it is now the first industry in the nation that the federal government is attempting to regulate *in toto*. This would seem to merit some examination in the bicentennial year. The issue is not yet settled although the advantage is clearly with the federal government. In any case the outcome will profoundly affect not only health care but the nation itself.

By way of background, the national interest in health care appears to have begun shortly after World War II when apparently unlimited dollars had helped to bring about dramatic achievements in both medicine and surgery. The Manhattan Project, also with unlimited dollars, had produced the atomic bomb which had ended the war—also dramatically. Given enough dollars it seemed that science could do anything. This belief led to a national commitment to the support of medical research which was wisely and productively administered primarily through the National Institutes of Health. The advances were significant, always highly publicized and often overstated. This gave rise to public pressures to bring more of this progress in medical research into day-to-day patient care. And once again it was assumed that all it would take to accomplish this would be dollars. But this was not to be so. Since 1965 federal dollars have been poured into health care with far less than expected improvement in the nation's health. Rather the overall result has been disaffection, dissatisfaction and runaway costs. Since there is no possibility of turning back (it would be unthinkable to take health care *away* from people) the federal government finds itself with a precarious hold on the tail of a monster that is largely of its own and the public's creation.

Unfortunately, but through no fault of its own, the federal government has a rather undifferentiated response to any unsolved or troublesome problems that it cannot or does not wish to ignore. Its response is to enact laws, make regulations and then bring its power to bear to force compliance. Often this works, but not always. When it does not, the undifferentiated response of the federal government is the same—pass more laws, make more regulations and try harder than ever to force compliance. This is what has happened in health care, and so far it has not been working well enough. As could have been predicted, the federal government is now mounting an all out effort by these same means to regulate every aspect of the health care industry—its personnel; its supplies and equipment; its facilities; its education, training and research, and its services and delivery systems. In short it seeks to regulate every facet of health care and the health care industry, because it really knows no other way to address so difficult and urgent a problem.

It is suggested that not only is this approach not working but, further, that it can never work well, if at all. Why? No doubt there are many reasons. A principal one may be that the nature of the health care system is such that it just cannot be regulated from outside of itself. The health care system of this nation is not the nonsystem that has been alleged. Rather it is an immensely complex and highly interdependent technological, social, economic and even political system. Anything that affects one segment quickly affects all the others. Its hallmark is the progress and change that are going on all the time. The health care system and its parts change even while they are being studied and even while standards are being developed to regulate them. This applies to facilities, education and research, as well as to personnel, patient care services, supplies, equipment and delivery systems. Fixed laws and well defined and well standardized government regulations are simply ill suited to govern such a dynamic and vital system. Laws and regulations just cannot be made or changed quickly enough to do the job. And the degree of standardization

that is necessary for efficient bureaucratic administration is in fundamental conflict with the nature of this kind of system and the way it has to operate.

Is there any analogy that might be a clue to what might be done? Perhaps there is. We might compare the health care system of today and the public pressures upon it with a biological system that lives and functions in relationship with its internal and external environments. There is much that is similar. In many ways the health care system is truly a living system. It is complex. Its parts are independent and autonomous in one sense, yet utterly interdependent in another. The system is always changing, and is often changed even by the process of being studied. It is affected by changes and forces in its environment and must adapt successfully to these to remain healthy and to function smoothly. It is notable that the governance or regulation of a biological system is primarily internal. It is external only in most unnatural situations and then the methods are crude at best—as when a cardiac pacemaker is implanted to regulate the heart beat. Certainly there is no example of every aspect of a complex biological system being successfully regulated from outside the system.

It is unlikely that there will be any sudden change in the approach of the federal government in its attempt to regulate the health care industry. It also seems unlikely that this approach can result in anything but an enormously increased internal friction (cost) within the system and reduced vitality and effectiveness (quality). The lesson to be learned will be both costly and painful to all concerned. If the analogy to a biological system is correct, the present approach can only fail, and a new one will sooner or later be needed. One can envision what this might be. It will entail (1) some means of internal governance within the health care industry which will recognize the relatively autonomous and independent parts within an increasingly interdependent system, (2) a means of adapting the internal environment of the health care system or industry to meet the requirements of the external environment of health care and (3) a new relationship with government which will allow the people in the health care industry some autonomy to govern themselves and to find solutions to the problems of health care as these may be defined—and this with the assistance of government rather than by direction from government.

In a sense this issue, which is now being hammered out in the crucible of health care, is whether the people, as represented in this case by the health care industry in all of its facets, can govern themselves within a framework of the requirements of an increasingly interdependent technologic, social, economic and political society. Or will they have to be governed and told what to do by persons in government who will rule them by passing laws and creating regulations—and using the power of the federal government to enforce them? This actually gets down to whether the people (and the health care industry is a substantial segment of the population) are to be the masters or the servants of their government.

The writers of the Constitution could hardly have foreseen how growing technological, social, economic and political interdependence would so challenge and threaten freedom and independence by this bicentennial year. The challenge and the threat are great indeed, but we can meet them if we have the will to do so.

—MSMW

Prenatal Diagnosis and Genetic Counseling

MEDICAL GENETICS has moved from an esoteric hobby of a few academic physicians to a variety of practical clinical applications. As young people acquire better information about human biology by courses in high schools and colleges and via the media, physicians increasingly face questions regarding problems in human genetics. The article by Dumars and associates in this issue of the JOURNAL attempts to provide some background and guidelines.

Genetic diseases can be divided into three broad categories: (1) Chromosomal disorders such as Down's syndrome, Turner's syndrome and others. Constitutional chromosomal disorders that affect chromosomes of all body cells must be differentiated from acquired chromosomal lesions in leukemia or other malignancies where abnormal chromosomes are only seen in the neoplastic tissue. (2) Mendelian diseases such as adult polycytic kidney disease, Huntington's chorea, sickle

cell anemia, cystic fibrosis and many others. (3) Multifactorial diseases caused by interaction of several genes and environmental factors. This category includes (a) common birth defects such as cleft lip and palate and neural tube defects; (b) common diseases of middle age such as diabetes, coronary heart diseases and hypertension, and (c) common psychoses such as manic-depressive disorders and schizophrenia.

Most mendelian diseases are individually rare but not uncommon as a group. Chromosomal disorders are relatively common (for example, Down's syndrome is found in one of 700 births), while the multifactorial disorders are most frequently encountered. Recurrence risks are highest for the mendelian disorders so that genetic counseling here becomes practically more important. Chromosomal tests are not useful in the workup of mendelian disorders since no detectable chromosome abnormalities are seen. In the multifactorial disorders, the recurrence risks are usually low (5 percent or less). Again, chromosome tests provide no help in diagnosis or counseling. While the recurrence risks for most congenital chromosome errors are quite low (approximately 1 percent), intrauterine diagnosis can lead to a specific diagnosis of fetal disease following chromosomal analysis of cultured amniotic cells. Hence, the practical importance of counseling in the chromosomal disorders. The patient mentioned by Dumars in this article with recurrence of classic Down's trisomy 21 syndrome had a 1 percent chance of this event recurring—a small but definite risk. Such rare misfortunes can be prevented by amniocentesis in all pregnancies following a previous child with Down's syndrome. Such a procedure will also detect recurrence of Down's syndrome in carriers of the rare translocation type of Down's syndrome. Identification of a translocation in a patient with Down's syndrome should be followed by chromosome study of the parents to detect the possible carrier state of translocation Down's syndrome in either father or mother. Fortunately, in most cases the translocation is a de novo event but in some families one parent is a translocation carrier. The chance that sibs of the carrier parent are also carriers is 50 percent. Detection of such carriers in relatives is done to identify those who require amniocentesis later.

Most amniocenteses are done prospectively in older mothers who have a relatively high risk (approximately 1 percent) of infants with Down's syndrome. The procedure has proved safe and relatively accurate in experienced hands and is strongly advised in all pregnancies of women beyond the age of 35 years. Amniocentesis usually provides assurance of a nonaffected child since most such tests show a normal chromosomal pattern.

Many autosomal recessive disorders such as cystic fibrosis cannot yet be diagnosed by intrauterine techniques. However, the number of diseases detectable by intrauterine diagnosis is increasing as the specific enzymatic defects in more disorders are being recognized. In these diseases, the procedure usually will be done following the birth of an affected child. Diagnosis of male sex by chromosomal analyses may be useful when female carriers for X-linked diseases such as hemophilia and Duchenne type of muscular dystrophy are pregnant. Vigorous search for female carriers in families with hemophilia and X-linked muscular dystrophy by antihemophilic globulin and creatine phosphokinase assays, respectively, is therefore indicated. Unfortunately, selective abortion of males in such circumstances will abort also 50 percent of normal males until specific diagnostic tests for these disorders are developed.

Alpha-fetoprotein determination of amniotic fluid will detect most neural tube defects such as spina bifida and anencephaly, making this test mandatory in women with a previously affected child who have a 3 to 5 percent recurrence risk. It may even become possible to screen all pregnant women for these defects by plasma α-fetoprotein levels which are elevated in many women carrying fetuses with neural tube defects. Placental puncture to obtain fetal blood is now becoming technically feasible as is hemoglobin analysis of the aspirated blood. The intrauterine diagnosis of sickle cell anemia and thalassemia major will therefore soon be practicable.

Patients should be informed that most genetic diseases cannot yet be diagnosed by amniocentesis and that a normal amniocentesis only rules out those diseases specifically searched for. Most inborn errors of metabolism are too rare and the tests too complicated to warrant multiple enzymatic tests on every amniotic fluid specimen. Chromosomal tests and α-fetoprotein detemina-tions, however, appear indicated on every specimen.

Genetic counseling should be made available whenever there is a significant recurrence risk of

genetic disease regardless whether the patient asks for such advice. Referrals to genetic counseling clinics may be indicated if the problem is complex. Genetic counseling requires knowledge regarding the nature and natural history of the disease. Often, similar appearing diseases may not be genetic at all or may be inherited by different mechanisms. The usual approaches to diagnosis such as careful history and physical examination in addition to full exploration of the manifestations of the disease in affected relatives together with laboratory and radiologic examinations will be necessary in the workup. There are no special genetic tests available in most instances. The good genetic counselor provides full understanding of the risks and burden of the disease to the family and explains all the reproductive options available. The final decision regarding future reproduction is made by the family involved. Most genetic counseling is done by medical geneticists in university and hospital centers. Nonmedical professionals trained in certain aspects of human genetics and counseling are increasingly working with MD geneticists and will have an important role to play in this field since not enough trained medical geneticists are available. Considerably more experimentation and trials of different organizations and modes of counseling will be required to elaborate an ideal scheme for genetic counseling. The satellite or outreach program which was worked out by the medical genetics unit at the University of California and which covers several areas of California is an interesting experiment of this sort.

As modern parents want their few children to be as healthy as possible, demands for genetic counseling will increase. All physicians therefore need to be conversant with the principles and recent advances in medical genetics.

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The Thalassemia Syndromes

DAVID WEATHERALL is the guru of that band of international thalassemologists who gather from time to time to ponder the many tantalizing aspects of this fascinating inherited disease. As Weatherall points out, the thalassemia syndromes are not at all rare. In fact, they constitute an international public health problem of staggering proportions. As many as 30 percent of the inhabitants of Cyprus are thought to be carriers of beta$^+$-thalassemia. Hence, it is estimated that 3 percent of all newborns on that island may be homozygotes. When one considers the treatment required to maintain life in such patients, the implications boggle the imagination of organizers of delivery of primary care.

Weatherall has ably reviewed the molecular genetics of thalassemia in his scholarly Paul Aggeler Lecture, which appears elsewhere in this issue, and has touched on the important clinical aspects as well. He emphasizes how the unbalanced globin chain synthesis in thalassemia creates a condition in which the total hemoglobin in the red cell is reduced. But, unlike the relatively simple hypochromic cell of iron deficiency, the thalassemia cell is further encumbered by accumulation of the unaffected globin chains produced in relative excess. These precipitate, damage the cell and thereby cause the massive ineffective erythropoiesis that creates the proliferative and hypermetabolic consequences of the disease. These useless red cells proliferate throughout the marrow, liver and spleen and even spread out from the vertebrae into the thoracic and abdominal gutters. The children die with terminal cachexia like patients ravaged with cancer. Indeed, the disease is often superficially indistinguishable from a chronic malignancy.

There is no need in this editorial to comment further on Weatherall's masterful review of the molecular biology, except to reemphasize how magnificently the data presented illustrate the vital interaction between the basic sciences and clinical medicine. Those who argue about the relevance of basic science should read and reread this fascinating story.

In the conclusion of his review, Weatherall proposes that the long-term hope for treatment of patients with thalassemia lies in "gene manipulation" as "the only feasible approach." This may

be true, but the way is fraught with very serious difficulties. In the vast majority of patients with beta thalassemia, the β gene is present but poorly transcribed. Hence, it might be possible to coax the errant gene into the production of messenger ribonucleic acid (RNA). But the mutation may make it impossible for any stimulation of transcription to be affected. Perhaps more likely is the possibility that the normal gamma genes may be stimulated to increase their rates of production. Finally, there are those who hope that normal globin genes wrapped up in plasmids might serve a therapeutic purpose. These are all approaches that are feasible and challenging, and as methods of growing erythroblasts *in vitro* become more practical, *in vitro* models of such systems will become testable at the bench. Their translation to the bedside will obviously take far longer.

In the meanwhile, constant reassessment of therapeutic approaches now at hand must be continued. Prevention through prenatal diagnosis is in fact a reality. Far more work is needed to render this procedure freer of obstetric hazards and more reliable biochemically. But there have been at least 30 such attempts carried out in London, New Haven, Boston and San Francisco, and most have been successful. Much of the impetus for this work comes from the laboratory of Dr. Y. W. Kan in San Francisco.

But, what can be done for the patients now at hand? Bone marrow transplantation is a logical thought, and the technical aspects are increasingly understood due in large part to the efforts of Drs. E. D. Thomas and Reiner Storb and their co-workers in Seattle. However, a decision to carry out a bone marrow transplantation in a very young patient with thalassemia would be extraordinarily difficult in view of the fact that conservative management should offer an 18 to 20 year life span for the patient as opposed to the 40 to 50 percent risk of immediate mortality due to the transplant procedure. Obviously, if one elects to do a marrow transplantation late in the course of life span of a patient with thalassemia, sensitization by transplantation antigens present in transfused blood will most assuredly compromise any hopes for success. Furthermore, the liver disease secondary to iron overload would notably increase the hazard of immunosuppressive therapy, particularly with cyclophosphamide. Transplantation certainly presents no easy solution at this time.

Only recently have investigators of the clinical aspects of the thalassemia problem begun to reexamine the basic precepts of care of these patients. Stimulated by the aggressive management techniques of Bernadette Modell, Elizabeth Letzky and their colleagues in London, a more quantitative examination of the problem of transfusion and elimination of iron overload has begun to emerge. Up to this time, it has been generally accepted that the most efficacious method of treatment of a patient with thalassemia is the elevation of the circulating hemoglobin concentration to at least 10 grams per 100 ml by transfusion. This accomplishes two purposes: the patient is afforded a higher oxygen carrying capacity and, more important, the massive proliferation of tne red cell mass is considerably reduced by this manipulation of the erythropoietin response. But the long-term consequences of this physiologic approach are disastrous because the iron overload induced by the red cell transfusions eventually results in intractable cardiac failure or arrhythmia.

Two approaches to the problem of hemosiderosis must be considered. First, and most obvious, is the development of effective chelation programs. Until very recently, the most promising drug, desferrioxamine, has been considered to be of little value because a single intramuscular dose of the drug induces only a small iron excretion. But recent studies have shown that prolonged administration of a standard dose of desferrioxamine may in fact induce very large rates of iron excretion. In recent studies carried out at the Children's Hospital Medical Center and the National Institutes of Health, as much as 80 mg of iron have been eliminated per day from such patients by the use of chronic subcutaneous administration of this drug. The desferrioxamine is delivered to the subcutaneous tissues of the anterior abdominal wall by means of portable infusion pumps which infuse a small but constant dose of the drug into the tissues at a constant rate.

Another approach follows a critical review of the problem of excess erythroid cell proliferation. We use transfused red cells to suppress marrow erythropoiesis in thalassemia, but it is entirely possible that certain chemotherapeutic agents might accomplish this necessary reduction of erythroid proliferation and would thereby enable the clinician to deliver less red cells to the patient. After all, the number of red cells required to provide sufficient oxygen carrying capacity for

a reasonably normal life is considerably less than that required to elevate the total hemoglobin concentration to 10 grams per 100 ml or more. Many patients with chronic anemia who are not encumbered by ineffective erythropoiesis exist very comfortably at hemoglobin concentrations of 6 to 8 grams per 100 ml. Whether the use of chemotherapeutic agents to reduce red cell proliferation would create unacceptable side effects is not known, and animal studies will be required fully to evaluate this type of approach.

At least as a result of continuous thinking about the thalassemia problem, novel approaches to therapy and prevention are in fact proceeding pari passu with the great advances in molecular biology reviewed here by Dr. Weatherall. As is true of all clinical approaches to difficult inherited disease, progress is slow. But it appears to be steady and occurring on several fronts. It seems likely that on the delightful occasion of Dr. Weatherall's next visit to San Francisco, even more advances in the molecular biology and treatment and prevention of thalassemia will be reported. Certainly many of these advances will be made by Western medicine.

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A New Challenge for Continuing Medical Education

RECENT LEGISLATION in a growing number of states seeks to link continuing medical education with evidence of continuing professional competence of a practicing physician. This is a most reasonable approach, but it poses a real challenge for both a practicing physician who must find the continuing education he may need to assure his own continuing competence, and for those who must provide the kinds of continuing education practicing physicians will need to remain competent in many specialties and in diverse settings.

There is a clear need for a more precise identification of just what it is that makes a physician competent—or not competent. There is obviously more to it than simply that he continues through a lifetime of practice the same kind of education that sufficed for graduation from medical school, for specialty certification or for licensure. For one thing, the requirements for these are generally considerably less differentiated than what may be needed for competence in a specific practice situation, and the busy practitioner has little time to waste learning things that he does not need to know. On the other hand, there are other kinds of things he should know to be competent in his own practice that were not taught in medical school. For example he should be aware not only of the drugs and technical procedures that might help a patient, but of the community resources that are available and how to use them.

A new challenge to continuing medical education would now appear to be to address the problem of just what is involved in the professional competence of a practicing physician in his own practice situation, and to set about making available continuing education that will enable every practitioner to assure his continuing professional competence in his own practice situation.

—MSMW

CASE REPORTS

Refer to: Weller MH: Bilateral eventration of the diaphragm. West J Med 124:415-419, May 1976

Bilateral Eventration of the Diaphragm

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DIAPHRAGMATIC EVENTRATION REFERS to absence or deficiency of diaphragmatic muscle, with resultant elevation. Bilateral diaphragmatic eventration is uncommon, and the prognosis is usually poor. The purpose of this report is to describe three cases and to review the roentgenographic appearance of bilateral eventration and the literature.

Reports of Cases

Case 1. A 2,180-gram boy was born at 37 weeks gestation after an otherwise uncomplicated pregnancy. There was immediate respiratory distress. The Apgar sore was 1 and 4 at one and five minutes respectively. Following endotracheal intubation, high ventilatory pressures were required. No bowel sounds were heard in the chest. The abdomen was scaphoid. Diaphragmatic hernia was suspected.

Results of initial arterial blood gas analysis included oxygen pressure (Po_2) of 49, an arterial carbon dioxide pressure (Pco_2) of 52 and a pH of 7.10. Arterial oxygen saturation was 75 percent. On a roentgenogram of the chest, pronounced elevation of both hemidiaphragms was seen, consistent with bilateral eventration. The stomach was in normal position (Figure 1). Despite maximum respirator settings, an arterial Po_2 above 50 could not be obtained. Right diaphragmatic plication was carried out at several hours of age. Postoperatively, the right lung would not expand to fill the pleural space (Figure 2). The infant died at 19 hours of age. Findings on postmortem examination confirmed elevation of both hemidiaphragms. Histologic examination of the diaphragm showed only collagen, with no muscle fibers. The lungs were hypoplastic and weighed a total of 10 grams. Microscopically, bronchi and alveolar ducts were seen, with only rare alveoli. Hyaline membranes lined many alveolar ducts. The vessels were thick and immature. Focal hemorrhage was present.

CASE 2. A 2,700-gram boy was born after a pregnancy complicated by mild polyhydramnios and premature rupture of membranes. The Apgar score was 5, both at birth and at three minutes. There was immediate grunting and cyanosis. Chest wall motion and lung ventilation were diminished, and there was obvious use of accessory respiratory muscles. Findings on arterial blood gas analysis showed a Po_2 of 55, a Pco_2 of 74 and a pH of 7.16. On radiographs of the chest, persistent right-sided diaphragmatic elevation was noted (Figure 3). Fluoroscopic examination showed restricted motion of both hemidiaphragms, but no para-

Figure 1.—(Case 1) Bilateral elevation of the diaphragm is present. The elevated dome of the left hemidiaphragm can be seen faintly just above the barium-filled fundus.

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doxical motion. Progressive atelectasis of the left lower lobe occurred despite manual ventilation. On day 14, a right diaphragmatic plication was carried out with only mild initial improvement, and subsequent diaphragmatic elevation. The infant died on day 30. Results of postmortem examination showed bilateral diaphragmatic eventration, bilateral pneumonia and interstitial fibrosis. There was no pulmonary hypoplasia. Findings were within normal limits on histologic examination of the brain stem, spinal cord, peripheral nerve and skeletal muscle.

CASE 3. A 2,948-gram boy was born by cesarean section for nonprogressive labor and ruptured membranes. Apgar scores were 3 and 5 at one and five minutes. Cyanosis, grunting, decreased thoracic excursion and decreased basilar breath sounds were noted. On arterial blood gas analysis, there was a Po_2 of 59, a Pco_2 reported at greater than 100 and a pH of 7.02. On a radiograph of the chest, elevation of both hemidiaphragms and bilateral lower lobe atelectasis were seen (Figure 4). The ribs and clavicles were thin, but there were no rib fractures. Skeletal survey disclosed overconstriction of the shafts of the tubular bones and diminished muscle bulk. Progressive central nervous system dysfunction occurred. A diagnosis of arthrogryposis multiplex congenita was made. Findings from a skeletal muscle biopsy were "compatible with neurogenic atrophy." The infant died at 15 days of age. On postmortem examination, bilateral eventration of the diaphragm was noted, worse on the right, which consisted mostly of fibrous tissue. The lungs weighed slightly less than normal and showed a mild lack of development of the periphery. Vessels and alveolar ducts extended to within two or three avleoli of the pleura. Skeletal muscle showed pronounced fibrous replacement. The brain stem, spinal cord and peripheral nerve were found to be normal.

Figure 2.—(Case 1) Postoperative radiograph of the chest made following right diaphragmatic plication. There is failure of expansion of the hypoplastic right lung.

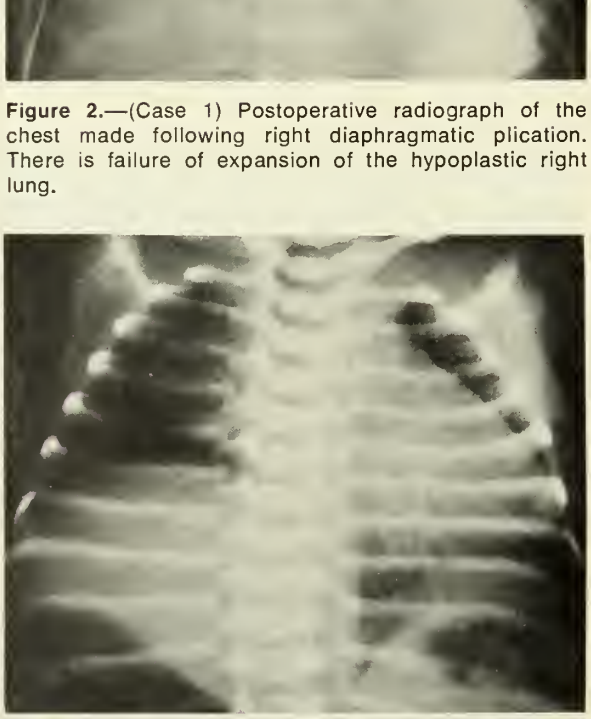

Figure 3.—(Case 2) Radiograph of the chest made during the first 24 hours of life showing elevation of the right hemidiaphragm. The left hemidiaphragm is not elevated but at autopsy was found to contain no muscle.

Discussion

Eventration refers to diaphragmatic elevation due to muscular deficiency. It is more often unilateral, and may present at any age.* Unilateral

*References 3-5,8,9,11-13,15,19-21,25-30,32,34,35

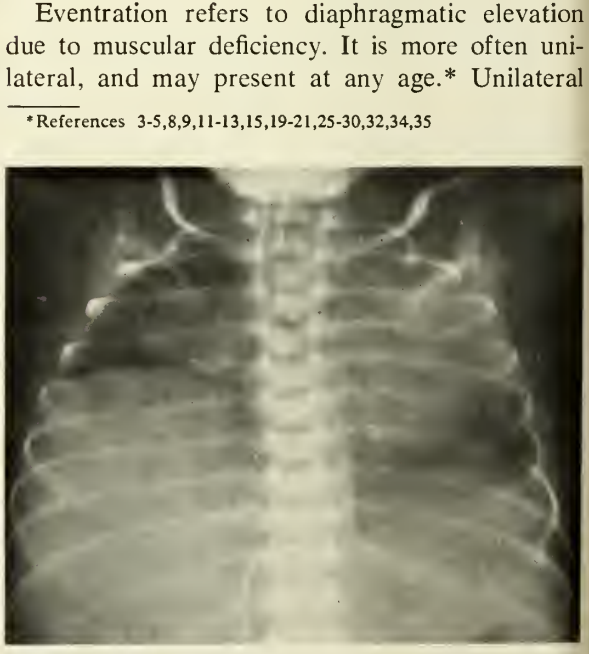

Figure 4—(Case 3) Radiograph of the chest made at 12 hours of age shows right diaphragmatic elevation. On subsequent radiographs, left sided elevation was seen as well. There is atelectasis involving both lungs. The ribs and clavicles have a slender, poorly ossified appearance.

TABLE 1.—*Review of Cases of Bilateral Eventration*

Author(s)	*Age*	*Sex*	*Onset of Symptoms*	*Symptoms*	*Radiologic Findings*	*Surgical Procedures*	*Pulmonary Hypoplasia*	*Comment*
Landon[19] 1936	4 wks	Male	Birth	Cyanosis, dyspnea	Chest x-ray: elevation of right hemidiaphragm. Fluoroscope: diminished diaphragmatic excursion on the right; normal excursion on the left.	No	....	Died day 80. Autopsy: right hemidiaphragm-peripheral muscle only. Left hemidiaphragm central fibrous membrane without muscle. Anomalous right lung fissures.
Avnet[1] 1962	5 days	Male	Birth	Transient respiratory distress, cyanosis (but had meconium staining)	Bilateral anterior eventration (pneumoperitoneography)	No	....	Died age 6 weeks. Autopsy: Potter's facies. Multiple congenital anomalies. Cerebral toxoplasmosis. Bilateral anterior eventration.
	10 mos	Male	....	Asymptomatic	Bilateral anterior eventration (pneumoperitoneography)	No	....	No follow-up. Angiocardiogram-coarctation aorta (mild)
Lundstrom and Allen[22] 1966	5 wks	?	....	Asymptomatic	Chest x-ray: elevation of left hemidiaphragm. Pneumoperitoneography: bilateral eventration	Yes; bilateral (staged)	....	Surgical findings: Diminished muscle anteriorly and laterally. ? absent spleen.
Firestone and Taybi[14] 1967	5 mos	?	5 mos.	Shortness of breath. Feeding difficulties	Bilateral anterior eventration (pneumoperitoneography)	Yes; bilateral	....	Died postoperatively. Autopsy: Bilateral anterior eventration, chronic pulmonary inflammation.
Wayne et al[37] 1973	3 days	Female	Birth	Labored respirations, mild cyanosis	X-ray film of chest: elevation of both hemidiaphragms. Bilateral pneumonia. Fluoroscope: diminished excursions of both hemidiaphragms	No	....	Died day 12. Autopsy: Congenital cytomegalovirus infection-urine and cerebrospinal fluid. Almost total aplasia of skeletal muscle of diaphragm with muscle fibers at periphery only. "Normal" phrenic nerves.
Briggs et al[7] 1973	2 hrs	Female	Birth	Respiratory distress, cyanosis	Elevation of right hemidiaphragm. "Small lungs," basal atelectasis	No	....	Died day 19. Autopsy: diaphragm shows no sign of muscle. Bilateral pulmonary hypoplasia. Congenital rubella.
Mellins et al[24] 1974	5 wks	Male	4 wks	Cyanosis, tachypnea	Bilateral anterior eventration	Yes	....	Died as 4 mos. Autopsy: eventration bilateral. Werdnig-Hoffmann disease.
	2 mos	Male	7 wks	Respiratory distress, cyanosis	Bilateral anterior eventration	Yes	....	Died at 5 mos. Autopsy: eventration bilateral. Werdnig-Hoffmann disease.
Weller 1975	Newborn	Male	Birth	Respiratory distress	Bilateral complete eventration	Yes	Yes	Died at 19 hours. Autopsy: No diaphragmatic muscle. Pronounced bilateral pulmonary hypoplasia.
	Newborn	Male	Birth	Respiratory distress, cyanosis	X-ray film of chest: elevation of both hemidiaphragms, right greater than left. Fluoroscope: diminished excursion bilaterally	Yes	....	Died at 1 mo. Autopsy: diaphragm contains no muscle on right, little muscle on left. Spinal cord, peripheral nerve normal.
	Newborn	Male	Birth	Respiratory distress, cyanosis	Bilateral complete eventration, basal atelectasis. Diminished peripheral muscle mass; thin gracile ribs and long bones	No	Mild	Died at 13 days. Clinical diagnosis: arthrogryposis multiplex congenita. Autopsy: absence of diaphragmatic muscle on right. Diminished muscle on left. Normal spinal cord, peripheral nerves. Atrophic muscles.

eventration is more common in males, and on the left side.[11,19,20,27,30,32] similar to diaphragmatic hernia. Respiratory distress is the usual presentation in the neonate.

Eventration is often confused with diaphragmatic hernia clinically and roentgenographically. The two may be impossible to differentiate surgically,[6,11] especially when abdominal contents are contained in a "sac" of parietal pleura and parietal peritoneum.[18] When eventration is present, there is an intermediate fibromuscular layer representing rudimentary diaphragm which may be difficult to identify. The clinical course is variable, and depends on the amount of diaphragmatic muscle and promptness of diaphragmatic plication. The prognosis in infants with unilateral eventration is guarded,[3,19-21,25,26,35] comparable to that of babies with acquired phrenic nerve paralysis.[11,15-17,29,33]

The details of the nine previous cases of bilateral eventration appear in Table 1. The three cases reported are similar in clinical and roentgenologic features. Respiratory distress and cyanosis began at birth. Diaphragmatic elevation was seen on radiographs of the chest. In two of the three infants, the right hemidiaphragm was more elevated than the left. Basal atelectasis was seen in two babies. Fluoroscopically, in the patient in Case 2 decreased diaphragmatic excursion bilaterally was seen. All three patients died, despite unilateral diaphragmatic plication in Cases 1 and 2. At postmortem examination, the diaphragm in Case 1 was found to have no muscle. The diaphragm in Cases 2 and 3 showed no muscle on the right and diminished muscle on the left. Of additional interest in Case 3 is the clinical diagnosis of arthrogryposis multiplex congenita, and the muscle biopsy consistent with neurogenic atrophy.

The cause of death in this disorder is unclear. Pulmonary hypoplasia is not a consistent postmortem finding. (Table 1). The lungs in Case 1 were severely hypoplastic. This baby had total absence of diaphragmatic muscle. There was no pulmonary hypoplasia in Case 2, and only mild hypoplasia in Case 3. With *partial* eventration, the cause of death is probably pneumonia, rather than pulmonary hypoplasia.

Etiology

The cause of eventration is unknown. A defect in embryogenesis is suggested by the presence of eventration in newborns and the fetus[2,23] and occurrence of frequent coincident anomalies.* Associated ipsilateral cephalad ectopia of the kidney,[8] and other abdominal organs,[5,36] similar to diaphragmatic hernia, support a defect in embryogenesis. The mechanism of muscularization of the primitive diaphragm is not clear. Diaphragmatic muscle may arise *in situ* from condensed mesenchyme.[38] Muscularization may also occur from posteriorly by invasion of cervical myotomes migrating with intact nerve supply.[19,26,35] If this process fails, absence of diaphragmatic muscle or incomplete anterior muscularization could result. Mechanical interference with bronchiolar differentiation could then eventuate in pulmonary hypoplasia. Finally, as the pleural spaces enlarge, chest wall muscle may contribute to muscular investment of the diaphragm.[6] Incomplete development of pleural spaces might lead to peripheral muscularization only, but cannot explain anterior eventration. Failure of myotome migration may lead to anterior eventration. Most patients with anterior muscle deficiency have been relatively asymptomatic, and have a longer survival.[1,14,22,24,27,35] In babies with early respiratory distress, there either is no diaphragmatic muscle or only peripheral muscle.[13,19,20,25] If failure of pleural "burrowing" is the responsible mechanism in these patients, pulmonary hypoplasia could be primary, rather than secondary.

Failure of peripheral nerve development may result in eventration.[5] The phrenic nerve has been noted to be absent,[15] small or normal in various reports.[5,11,25,30,32] Partial eventration occurs with arthrogryposis multiplex congenita,[12] and a disease in sheep, similar to human arthrogryposis, shows evidence of muscular aplasia of the diaphragm.[2] Two patients with bilateral anterior eventration subsequently died of central nervous system disease at five and seven months of age.[24] In Cases 2 and 3, the brain, cervical cord and peripheral nerves showed no evidence of anterior-horn cell disease. In Case 3, findings in a premortem skeletal muscle biopsy were "compatible with neurogenic atrophy."

Congenital infection has been linked with eventration. There are reports of associated congenital rubella,[7] cytomegalovirus infection[37] and cerebral toxoplasmosis.[1] Perhaps viral or parasitic infection in utero affects central or peripheral nervous development resulting in neurogenic atrophy of the diaphragm. Death may occur before development of peripheral muscle disease.

*References 1,4,11,20,21,25,32,35

Summary

The three cases reported are similar radiographically and confirm the uniformly dismal prognosis of bilateral eventration when symptoms are present at birth. The cause is probably a defect in embryogenesis, although the roles of central and peripheral diaphragmatic innervation, and of congenital infection are still unclear.

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Mitral Valve Vegetation Simulating Left Atrial Myxoma

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THE ECHOCARDIOGRAPHIC appearance of vegetations in patients with endocarditis was first described by Dillon and associates in 1973.[1] Several subsequent reports have substantiated the important role of echocardiography in the diagnosis of endocarditis involving the aortic valve.[2-4] Considerably less has been written on the echocardiographic pattern of mitral valve vegetations. We recently saw a patient with mitral valve endocarditis in whom findings on an echocardiogram initially suggested the presence of a left atrial myxoma. The subsequent disappearance of the abnormal echoes concomitant with effective medical treatment of the endocarditis suggests that the mass of echoes noted represented a vegetation attached to the mitral valve.

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Submitted July 18, 1975.

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Report of a Case

A 30-year-old man—who had a history of the intravenous use of drugs—was admitted to San Francisco General Hospital for treatment of a swollen arm. An area of tenderness had developed over the left forearm near the site of intravenous injections four months earlier. The area became red and swollen and two weeks before admission a draining ulcer was noted; chills and weight loss did not occur.

The temperature was 103°F (39.4°C), heart rate 92 beats per minute and blood pressure 136/86 mm of mercury. The neck veins were not distended, the chest was clear and the heart tones were normal with no audible murmur. The spleen could not be palpated. There were no petechiae. Cellulitis was noted to be present over the dorsal aspect of the left forearm with a central 1 cm ulceration and surrounding induration without fluctuation. The hemoglobin value was 10 grams per 100 ml and leukocyte count 16,000 per cu mm with 80 percent neutrophils, 15 percent lymphocytes, 4 percent monocytes and 1 percent eosinophils. On analysis of the urine, there were three to four leukocytes per high power field and no red blood cells. Serum creatinine was 1.2 mg, albumin 3.1 grams and globulin 5.1 grams per 100 ml. No abnormalities were noted on an electrocardiogram and roentgenograms of the chest. Wound debridement was carried out and penicillin therapy, 10 million units daily, given intravenously, was begun. Cultures from the wound grew Serratia marcescens, Staphylococcus aureus and enterococcus. Two blood cultures were sterile.

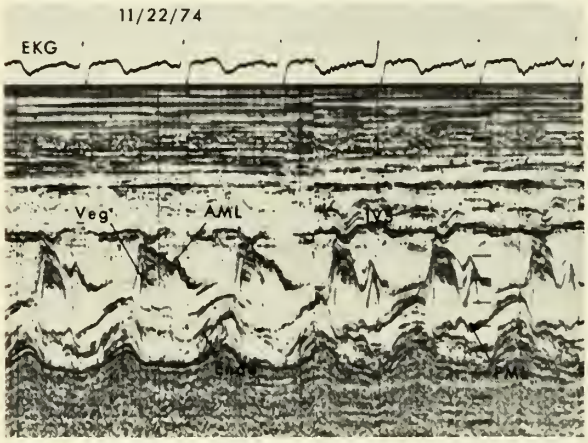

Figure 1.—Echocardiogram on day 14. A dense mass of echoes appears behind the anterior mitral leaflet shortly after onset of diastole. Note flattening of E to F slope of anterior leaflet, especially evident in second and third complexes. Veg=vegetation, AML=anterior mitral leaflet, PML=posterior mitral leaflet, IVS=interventricular septum, Endo=endocardium.

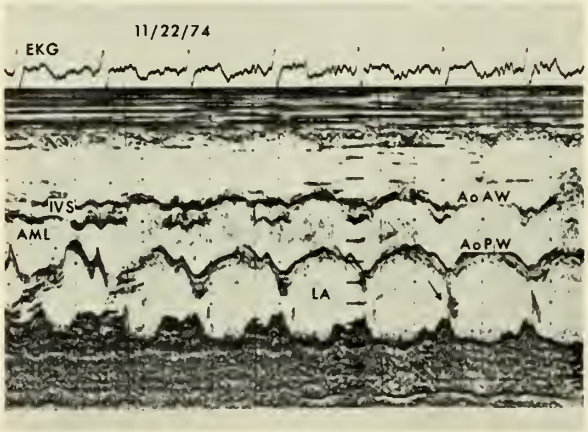

Figure 2.—Echocardiogram on day 14 showing sweep from mitral valve up to aortic root. Abnormal echoes (↘) are present in left atrium in early systole (compare with Figure 5B). AoAW=anterior aortic wall, AoPW=posterior aortic wall, LA=left atrium; see Figure 1 for other abbreviations.

Low grade fever persisted. A soft apical holosystolic murmur was heard on day 8. Repeat cultures of blood from the femoral vein grew enterococcus. On day 9, an abscess at the wound site was incised and drained. The patient became afebrile on day 11, and the positive blood culture was thought to be contaminated. Administration of penicillin was discontinued. On day 14, splinter hemorrhages occurred, fever recurred and the apical murmur was louder. Echocardiography was carried out (see subsequent section). Treatment was initiated with ampicillin, 3 grams every four hours given orally, and streptomycin, 500 mg given intramuscularly twice daily; repeat blood cultures grew enterococcus. Echocardiography was repeated every two weeks. The patient became afebrile on day 18. The holosystolic apical murmur persisted unchanged. No gallop or symptoms of cardiac decompensation developed. The patient was discharged on day 53.

Echocardiograms

A Unirad Series 100 echocardiograph with a 2.25 megaherz transducer focused at 7.5 cm was used, interfaced with an Electronics for Medicine DR8 Strip Chart Recorder. The initial echocardiogram obtained on day 14 showed a dense mass of echoes that appeared just behind the anterior leaflet of the mitral valve shortly after the onset of diastole but was not present during systole (Figure 1). A sweep up to the aortic root (Fig-

ure 2) showed abnormal echoes in the left atrium in early systole. The appearance of these atrial echoes was more in keeping with the pattern of ruptured mitral chordae than that of a prolapsing tumor (see Figure 5). Repeat echocardiograms taken over the ensuing six weeks showed gradual diminution of the abnormal block of diastolic echoes (Figure 3).

Discussion

The long history of intravenous drug use, septic abscess, multiple positive blood cultures, splinter hemorrhages and changing pathologic murmur unequivocally indicated bacterial endocarditis in this patient. The echocardiogram supported the clinical impression of mitral valve involvement, but raised the possibility of a left atrial myxoma.

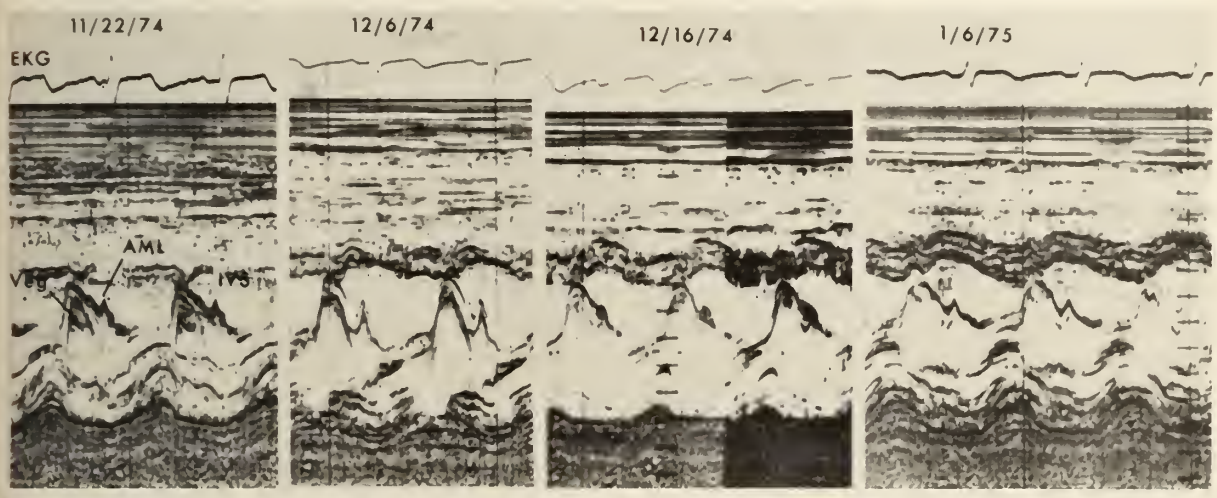

Figure 3.—Serial echocardiograms of mitral valve at approximately two week intervals. There is a gradual diminution of the abnormal block of diastolic echoes. See Figure 1 for abbreviations.

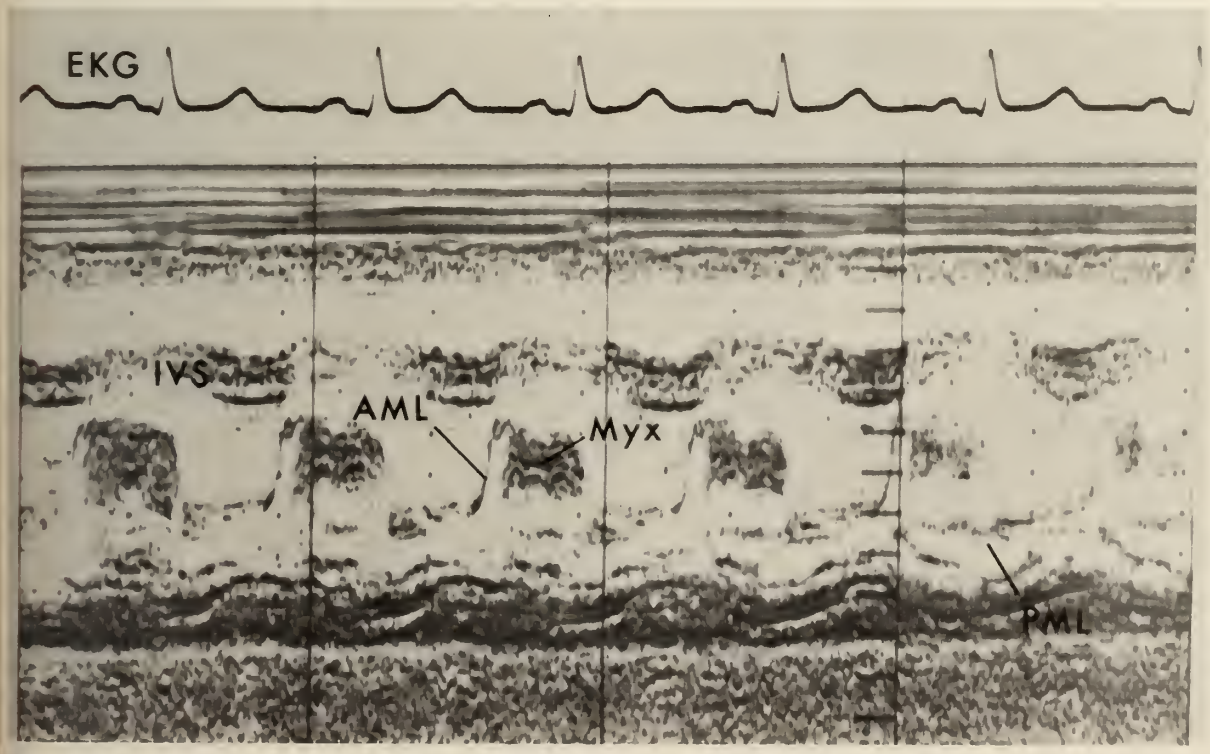

Figure 4.—Echocardiogram from 33-year-old woman with left atrial myxoma confirmed at surgical operation. A mass of parallel echoes appears behind the anterior mitral leaflet shortly after onset of diastole. Note flattened E to F slope of anterior leaflet (see Figure 5A). Myx=myxoma; see Figure 1 for other abbreviations.

Endocarditis associated with an atrial myxoma is known to occur,[5-7] one case occurring at our hospital.[7] The progressive diminution in the size and intensity of the abnormal echoes that occurred concomitantly with effective antimicrobial therapy and the absence of evidence of further embolic episodes support the contention that the block of echoes represented a vegetation and not a left atrial myxoma.

There have been many descriptions of the echocardiographic appearance of left atrial myxomas.[8-17] Pathognomonic features are generally thought to be (1) the appearance soon after the onset of diastole of a mass of parallel echoes immediately posterior to the anterior mitral leaflet (Figures 4 and 5A), (2) flattening of the diastolic (E to F) slope of the anterior mitral leaflet, frequently accompanied by an obscuring of the posterior mitral leaflet and (3) appearance of abnormal echoes in the left atrium during systole, representing prolapse of the tumor through the mitral orifice. Dillon and co-workers[1] in describing the appearance of three infected mitral valves called attention to the fact that the abnormal echoes appear to be "attached" directly to the mitral valve leaflet(s), whereas in the case of a left atrial myxoma the abnormal echoes appear "detached" from the valve. They also stressed the importance of demonstrating the presence of abnormal echoes in the left atrium when making the echocardiographic diagnosis of a left atrial myxoma. In the initial echocardiogram of our patient, the abnormal mass of echoes did indeed appear detached from the mitral valve. In addition, abnormal echoes were present in the left atrium, further suggesting the possibility of a myxoma. Probably the vegetation was, in fact, prolapsing through the mitral orifice. The pattern of the echoes in the left atrium (Figure 2) is identical to that which we have seen in two patients with endocarditis and ruptured chordae to the anterior mitral leaflet (Figure 5B).

There is one other description in the literature to date of a mitral valve vegetation that mimicked echocardiographically a left atrial myxoma.[18] In this case, the patient had underlying rheumatic mitral stenosis.

Summary

Echocardiographic examination of a 30-year-old man with endocarditis involving the mitral valve showed a pattern suggestive of left atrial

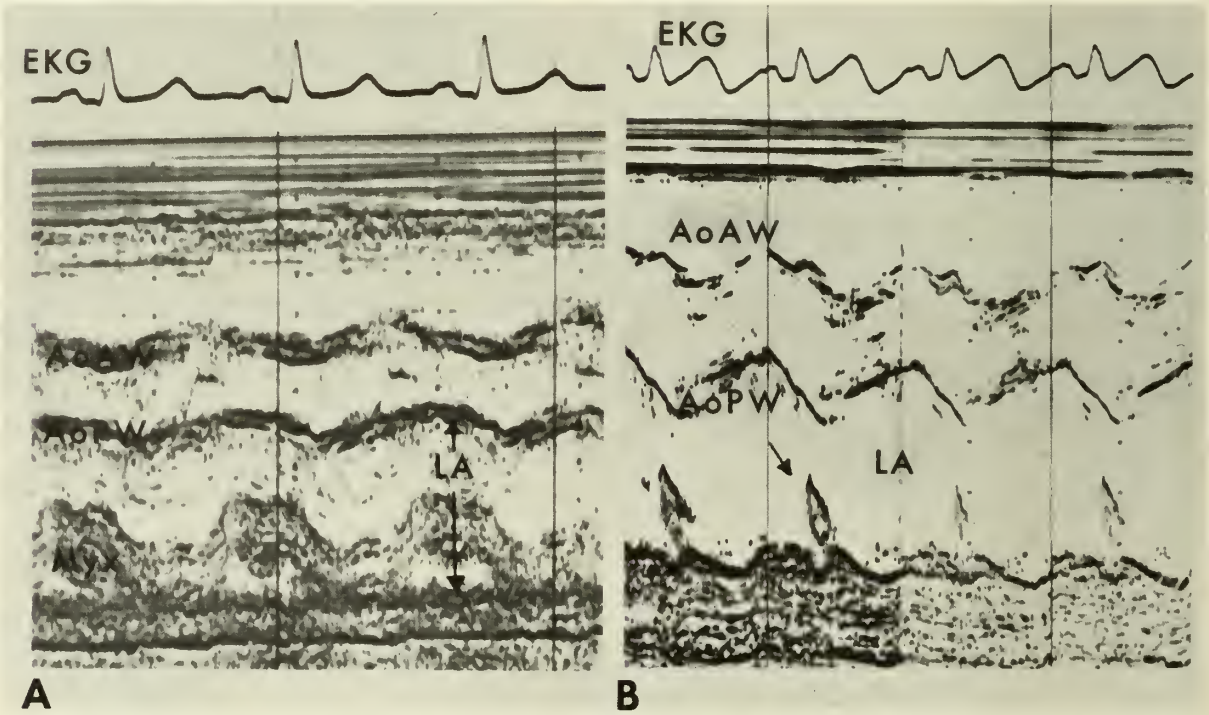

Figure 5.—**A**, echocardiogram from the same patient as in Figure 4 showing block of echoes in the left atrium representing a myxoma. **B**, echocardiogram from 35-year-old woman with ruptured chordae to anterior mitral leaflet confirmed at surgical operation. Arrow points to echoes in early systole thought to represent mitral valve or chordae projected into left atrium during ventricular contraction, or both. Note similarity to Figure 2. See Figures 1, 2 and 4 for abbreviations.

myxoma. The abnormal echoes diminished dramatically during antibiotic therapy over the ensuing six weeks and probably represented a vegetation prolapsing through the mitral orifice. Echographic features considered pathognomonic for left atrial tumor may be shared by mitral valve vegetations.

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Refer to: Bellville JW, Swanson GD, Miyake T, et al: Respiratory stimulation observed following ethanol ingestion. West J Med 124:423-425, May 1976

Respiratory Stimulation Observed Following Ethanol Ingestion

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ETHANOL IS REGARDED as a central nervous system depressant. Its sedative effect and its effects on psychomotor performance have been studied in detail. Recently its respiratory depressant effects have been shown to be dose related, that is, as the dose of ethanol is increased its respiratory depressant properties are enhanced.[1,2]

This report summarizes our findings in a young man who has an unusual response to ethanol in that it produces respiratory stimulation and the degree of respiratory stimulation appears to be poorly related to the dose of ethanol ingested.

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Submitted July 18, 1975.
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Methods

These studies were done in a 25-year-old healthy man during the course of an investigation of the respiratory effects of pentobarbital, Δ9-tetrahydrocannabinol and ethanol. The basic method for measuring respiratory depression or stimulation has already been described by us previously[3] and represents a modification of the rebreathing technique of Eckenhoff and co-workers[4] except that the rebreathing reservoir is charged with 5 percent carbon dioxide in oxygen as suggested by Read.[5] The volunteer subject was allowed his usual meals, but it was requested that coffee and tea as well as alcoholic beverages be omitted for the preceding 12 hours.

The subject was fitted with a rubber metabolic mouthpiece and nose clip. While in a semireclining position, he breathed through the apparatus for from three to five minutes to become accustomed to it. Then the system was closed and rebreathing begun, continuing for 10 to 12 minutes. At the end of this time, his minute ventilation was at least 30 liters per minute. Simultaneously respiratory response curves were plotted automatically by an analog computer, and a point was plotted for each breath representing the end-expiratory carbon dioxide rate and the ventilation for that breath (Figure 1). This value was also stored in a PDP/8 computer (Digital Equipment Corporation) for analysis. Following the completion of the response curve determination, a least mean square line was fit and the intercept at 20 liters per minute and slope were printed out as well as

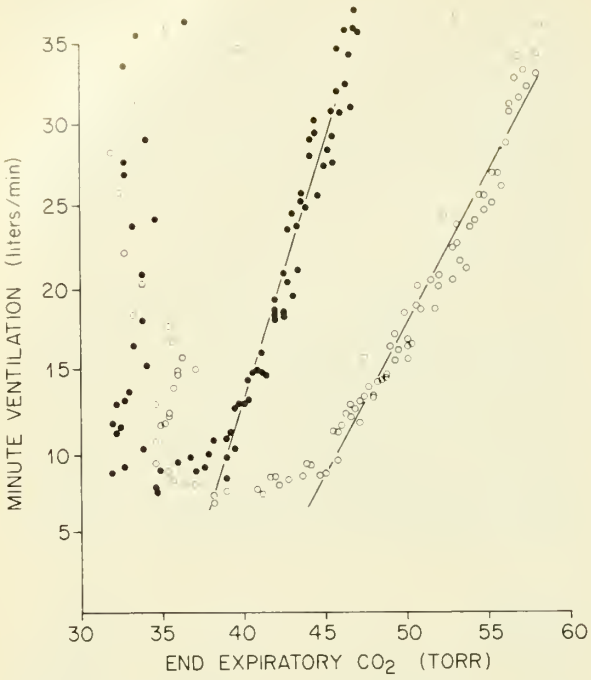

Figure 1.—End-expiratory carbon dioxide is plotted versus minute ventilation. The open circles represent a control determination while the solid circles show the results ½ hour following administration of 120 ml of 80 proof vodka. A least mean square line was fit to the rebreathing data. The control slope was 1.84 liters per minute per torr of carbon dioxide pressure while the ½ hour slope was 3.20. The correlation coefficients were 0.98 and 0.97 respectively. The off transient is also plotted.

the correlation coefficient and the number of breaths analyzed. After two control runs had agreed within 0.5 torr* of carbon dioxide pressure (P_{CO_2}), the test medication in the form of 80 proof vodka in fruit juice was administered.

Displacement was determined as the change from the average of all the control curves in the intercept at a ventilation of 20 liters per minute of the best fitting least mean square line through the response curve. Negative values indicate a shift to the left (respiratory stimulation) of the control curve.

Results

Typical respiratory response curves are shown in Figure 1 for a control and after administration of ethanol determination. The carbon dioxide response curve displacement results are summarized in Figure 2 in which is plotted the response curve displacement versus time at various doses of 80 proof vodka ranging from 30 to 180 ml given in fruit juice. It is apparent that as the dose is increased, the respiratory stimulation is not notably increased. Also shown is the response after a drug that is a known respiratory stimulant, aspirin (990 mg given orally). We did not plot a dose-effect curve for ethanol since it is apparent that at the higher doses of vodka the subject was not observed for a long enough period of time to define a complete time effect curve. In Table 1 are the data for the respiratory response curve slopes corresponding to the displacement data shown in Figure 2. With displacement of the response curve to the left there was an increase in slope.

*One torr is equal to 1 mm of mercury.

Discussion

Although ethanol has been shown to be a respiratory depressant we have observed in several persons that it may have respiratory stimulant properties. One of these persons was Jewish while the one in whom the most pronounced reaction was seen and who is reported here was of Japanese descent.† Recently attention has been called to the unusual responses seen in Oriental adults who drink ethanol and in whom a characteristic flushing of the face is seen. This was recently discussed by Wolff[6] and studied in more detail by Ewing and associates.[7] Ewing and co-workers showed that the production of acetylaldehyde is higher in these Orientals than in Caucasians who do not have this flushing response.

The subject who participated in this study had the characteristic flushing of the face and reported a tightness in his chest following the ingestion of ethanol. Furthermore, neither he nor his father was accustomed to ingesting ethanol and reported they did not enjoy alcoholic beverages. The subjective responses reported by this volunteer are similar to those reported by Ewing.

These data suggest that some persons have an

†Recently we studied this man's cousin in whom pronounced respiratory stimulation and flushing also was seen following ingestion of 30 ml of vodka.

TABLE 1.—*Slope of Respiratory Response Curve in Liters per Minute per Torr of Carbon Dioxide Pressure*

Ethanol Dose (ml) 80 Proof	*Average Control*	*1/2*	*1*	*2*	*3*
30	1.33	1.40	2.14	0.68	1.30
60	2.16	2.35	2.14	2.32	2.01
60	1.83	2.62	2.56	2.01	1.67
60	1.72	2.43	2.30	2.76	2.31
90	2.26	3.04	2.32	2.18	2.12
120	1.68	3.20	2.48	2.59	2.22
180	1.96	2.45	3.11	2.35	2.46
Aspirin 990 mg	1.85	1.95	2.16	1.97	2.10

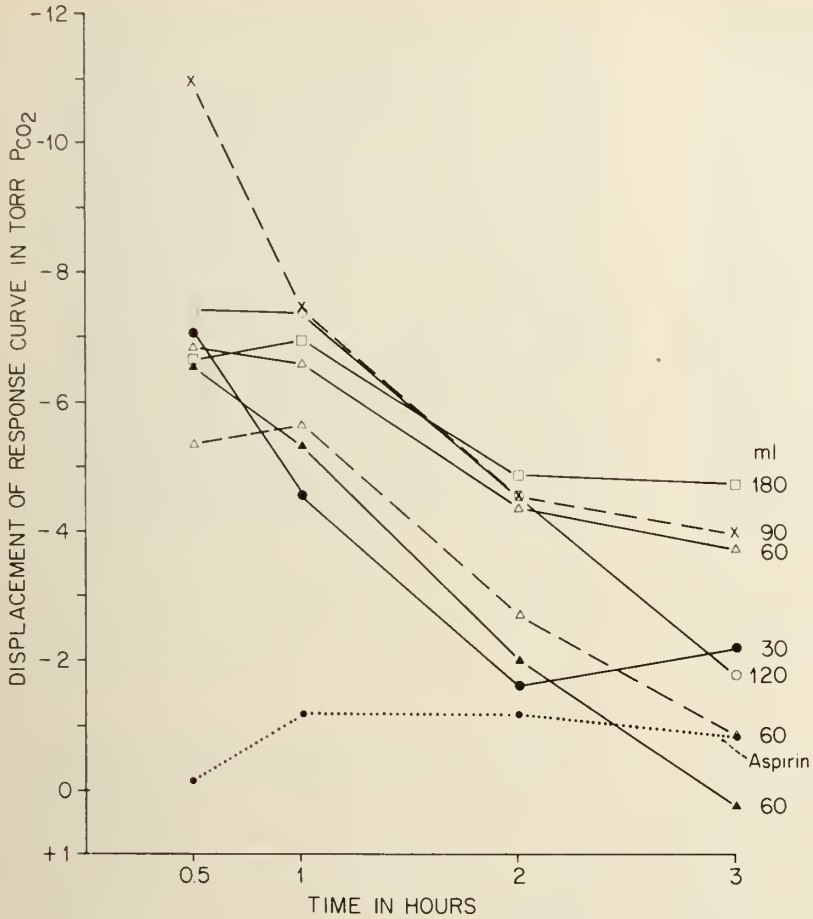

Figure 2.—Time-effect curves following various doses of 80 proof vodka as well as aspirin (990 mg) given orally are shown.

unusual response to ethanol and that it not only causes the previously reported flushing of the face but acts as a notable respiratory stimulant. The pharmacologic basis of these effects has not been defined and although acetylaldehyde production has been shown to be higher among these people, we do not know if the respiratory stimulation is due to acetylaldehyde or some other metabolite cr hormone. Certainly the degree of respiratory stimulation is dramatic when compared to other mild respiratory stimulants such as aspirin (Figure 2) or caffeine.[8]

Clearly pharmacologic factors produce this pronounced effect. The large change in respiratory response cannot be explained by physiologic factors such as change in ventilatory mechanics. We believe that an understanding of this phenomenon might aid in explaining why some people do not tolerate alcoholic beverages. We agree with Ewing and co-workers that "cultural explanations will not suffice to explain the phenomena we have observed. Indeed, it is possible that drinking patterns in a culture are built upon a physiologic foundation."

Summary

Some ethnic groups notably do not abuse ethanol. We have observed in a volunteer who is of Japanese descent, in addition to a previously described flushing of the face seen in some Orientals, a pronounced respiratory stimulation following ingestion of alcohol. This gives strong support to the hypothesis that pharmacologic factors are important in lack of ethanol abuse seen in these persons.

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Amebic Hepatic Abscess: Demonstration by Total Body Opacification and Tomography

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INFESTATION BY THE protozoon Entamoeba histolytica has a worldwide tropical and semitropical distribution. Although rare in the United States, the disease appears sporadically in travelers and immigrants.

Encysted forms of the organism enter the intestinal tract via contaminated food. Within the terminal ileum and colon the cyst changes into the invasive trophozoite. In a small percentage of patients, the organisms migrate through the intestinal wall, enter the portal venous system and lodge in the liver. Presumably by enzymatic action, the trophozoites produce a focal area of liver necrosis. A zone of intense inflammation surrounds the abscess.[1] In an army hospital, Isaac[2] found liver disease in 14 percent of 222 patients with amebic dysentery.

In their study of 263 patients, DeBakey and Ochsner[3] noted that most amebic abscesses were single and occurred in the right lobe. In only a quarter to a third of the cases were ameba shown to be present in the stool. Common clinical manifestations were hepatic pain and tenderness, hepatomegaly, weight loss and weakness. Diarrhea occurred in about two thirds of the cases. For reasons unknown, amebic hepatic abscess develops predominantly in men.[4,5]

Material and Methods

Two patients with clinical findings and photoscintigraphic changes suggesting amebic liver abscess were examined by total body opacification and tomography of the liver. Two ml per pound of body weight of 25 percent sodium diatrizoate in a 100 ml 5 percent glucose solution was infused over a ten minute period. At the completion of infusion, radiographs are obtained using a circular motion (zonography) at 2 cm intervals in the anteroposterior or right posterior oblique projection. After localization, a single lateral tomogram determined the depth of the abscess.

Case Reports

CASE 1. Until one year before admission, this 21-year-old man had lived in Mexico. He complained of a sharp, nonradiating, persistent right upper quadrant pain of six days duration, accompanied by intermittent fever. His pain was aggravated by deep inspiration, sitting up and abrupt movements. He reported recurrent diarrhea and that other family members had episodic diarrhea. The examining physician found right upper quadrant tenderness which increased with deep inspiration.

On admission, laboratory studies disclosed an hematocrit of 35 percent, leukocyte count of 13,000 per cu mm with 54 percent neutrophils. Protein was 7.8 grams per 100 ml, albumin-globulin ratio 2.3, bilirubin 1.3 mg per 100 ml, lactic dehydrogenase 155 IU per liter, alkaline phosphatase 181 IU per liter, serum glutamic oxalic transaminase 0.42 IU per liter. Tests of stool were negative for ameba. Indirect hemagglutination titer for amebiasis was positive at 1:2048 (diagnostic titer 1:128).

Sigmoidoscopy showed a hyperemic rectal mucosa. The pathologist found chronic inflammation but no trophozoites in the biopsy specimen.

On plain films of the abdomen, the liver edge was seen to be low and rounded. The chest radiograph showed an elevated right hemidiaphragm and a right lower lobe infiltrate. Intravenous cholangiogram showed a normal common duct. A filling defect in the lower portion of the right liver lobe was found on Te99m scintiphoto. On total body opacification with tomography, it was noted that a large, oval, radiolucent abscess with surrounding zone of increased vascularity occupied the lower aspect of the right lobe of the liver (Figure 1). Findings on a B-mode ultrasound scan confirmed a sonolucent defect in the same area of the liver. Occasional internal echos were considered due to debris inside a fluid filled mass.

A clinical diagnosis of amebic abscess was made and administration of metronidazole, 750

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Figure 1.—Total body opacification with liver tomography. Right posterior projection. Large oval radiolucency in the lower portion of the right lobe represents the amebic abscess. (arrows) A zone of hyperemia surrounds the abscess.

Figure 2.—Total body opacification with liver tomography. Anterioposterior projection. The avascular amebic abscess is present immediately beneath the diaphragm in the dome of the right lobe. (arrows) A hyperemic wall demarcates the abscess.

mg three times a day, was carried out for ten days. With this treatment the fever resolved, the abdominal pain decreased and the liver size diminished.

Case 2. The patient, a 37-year-old man, a Mexican national, had complaint of fever and chills. There was pain in the right shoulder, increasing on deep inspiration and right-upper-quadrant palpation.

The patient was anemic with an hematocrit of 32.2 percent, leukocyte count 10,000 per cu mm with 68 percent neutrophils. On tests, a specimen of stool was guaiac positive. Indirect hemagglutination for amebiasis was positive at 1:4096, (diagnostic titer 1:128), bilirubin was 0.3 mg per 100 ml, alkaline phosphatase was 300 IU per liter.

On liver scintiphoto with Te99m, a large defect was found in the posterior, superior aspect located adjacent to the diaphragm. A B-mode scan showed the lesion to be echo-free.

With total body opacification using 150 ml of 25 percent diatrizoate in an equal amount of glucose solution, tomography confirmed the presence of the abscess in the superior posterior portion of the right liver lobe (Figure 2). A hyperemic zone was noted surrounding the abscess.

The patient was treated with metronidazole, 750 mg three times a day, for ten days. After four days he became afebrile. He was discharged in a greatly improved condition but was lost to follow-up.

Results

In each patient, total body opacification and tomography showed the existence of and the location of the amebic hepatic abscess suspected from clinical findings and radionuclide liver scan. Although no ameba were shown in specimens of stool, there were positive indirect hemagglutination titers in both cases and symptoms ceased in both on administration of metronidazole. Juniper and co-workers[6] have shown the indirect hemagglutination test to give positive findings in 88 percent of patients with amebic liver disease.

Discussion

In 1963 O'Connor and Neuhauser[7] introduced the concept of total body opacification for the study of abdominal masses in children. Subsequently, Wendth[8] and Schenker and associates[9] used infusion nephrotomography to show the presence of renal masses. In 1970 Genereaux and Tchang[10] employed total body opacification in the diagnosis of obstructive cholecystopathy, considering it a safe, simple and reliable procedure.

Morgan and Johnson[11] and Hatfield and Pfister[12] applied total body opacification with tomography to masses situated within the liver and spleen. Both groups noted that the technique allowed differentiation of solid and cystic masses. Mitty and Schapira[13] showed liver cyst, abscess and metastasis; and Kurti and Patel[14] diagnosed

adrenal cysts by this technique. Love and associates[15] used infusion tomography to show pelvic tumors in women.

The infusion of 2 ml per pound of body weight of 25 percent diatrizoate solution fills the blood pool, temporarily opacifying large vascular organs such as the liver, spleen and kidney. Necrotic lesions caused by diminished vascularity appear as lucent defects within the organ. Hyperemic contiguous tissue provides a surrounding zone of increased opacification.

Before radionuclide imaging came into use, the diagnosis of amebic liver abscess depended on clinical findings and secondary changes in the chest; pleural effusion, basal pneumonitis and limited hemidiaphragm excursion.[16] Radionuclide imaging based on phagocytosis of radioactive colloidal particles by the reticulo-endothelial cells allowed a study of the liver structure, enhanced the reliability of the diagnosis of liver abscess and reduced the morbidity and mortality.[17-19] Serial photoscintiscans also provide a means of following the response of the abscess to medical treatment.[20]

With a dose of 10 millicurie of 99mTe sulfur colloid, the patient receives a whole body dose of 166 millirad and a liver dose of 5.3 rad.[21] By comparison, a series of six liver tomograms would give an approximate skin dose of 3.6 rads, a gonadal of 600 millirad in a female patient and, with proper shielding, no gonadal dose in the male.[22]

Nuclear imaging has an inherent sensitivity limitation in that lesions smaller than 2 cm at a depth of 10 cm cannot be detected by the gamma camera.[23] For all liver lesions, the overall accuracy of liver scan is 77 to 84 percent in studies where the diagnosis could be confirmed by autopsy or biopsy.[21] The photoscintigram does not allow differentiation of cyst, abscess or avascular tumor within the liver.

B-mode ultrasound scanning of the liver does not delineate small lesions. Ultrasound has the advantage in that it involves no biologically deleterious radiation and permits the examiner to discriminate between a solid and a fluid-containing lesion.[24]

In a patient with amebic colitis and suspected amebic liver disease, total body opacification with tomography provides a rapid and readily available means of showing the presence of an intrahepatic abscess. Infusion tomography can supplement and confirm the findings of a photoscintigram of the liver and B-mode ultrasound scan examination. If the latter methods are not available, infusion tomography can serve as a reliable substitute.

Summary

The technique of total body opacification and tomography confirmed the presence of amebic liver abscess in two patients. Technetium 99m liver scan and B-mode ultrasound also showed the abscesses. Although ameba were not recovered from stool specimens, there were in both cases high titer indirect hemagglutination findings on tests for amebiasis and in both recovery occurred on administration of amebicidal medication.

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Special Article

Caring for Families of High-Risk Infants

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THE USE OF intensive care nurseries has caused a major improvement in the quality of care for ill newborn infants and has resulted in a lowering of neonatal mortality. This drop in mortality has been in addition to a decrease in the long-term morbidity of premature and term infants.[1-4] Continuing research and application of newer discoveries are responsible, as well as the rapid dissemination of this information from one facility to the next. Although the specific details of managing certain classes of problems such as hyaline membrane disease, hypoglycemia and erythroblastosis may vary from one institution to another, the general protocols involved and methods of approach and treatment are fast becoming standard. At present the similarities are greater than the differences.

However, one great variability remains in the interaction of family, specifically the parents, and the medical personnel involved in the case of an acutely ill neonate. In fact, different approaches to such interaction may be seen not only from facility to facility but also within the same hospital. A standard approach, as used for an acute medical problem, has not been developed for the care and attention delivered to the families involved. There is evidence, though, that attempts are being made to achieve that goal.[5-10]

The causes of the problem are many and do not necessarily result from reluctance by medical staffs to establish communication with parents. In fact, many causes of the problem stem from parental hesitancies. Inadequate interaction between parents and staff that can be traced to the parents may be the result of (1) an actual desire by parents not to be made aware of the severity of the problems involving their baby or a denial that a threat to life exists, (2) each parent, wishing to protect the other from potentially distressing news, may choose not to solicit any information from the staff and (3) there may be a desire by the parents, as recovery occurs and survival becomes apparent, to remain uninformed about early critical events in the life of their baby because of the threat it poses to the baby's future growth and later development.

Similarly, the medical staff may show hesitancy in talking freely with parents for many reasons: (1) the difficulty physicians and nursing staffs have in expressing probabilities to parents —that is, even though they may be hopeful of survival there remains the constant threat of death, (2) with recovery there is a tendency to become more involved with insuring that the baby is thriving and that the parents should be more concerned with the daily feeding and care problems than the difficulties through which the baby passed perinatally and (3) finally and most important, there may be a lack of knowledge by house staff members as to what long-term "quality of survival" can be expected for infants who have had serious and life threatening perinatal experiences and who have been cared for in newborn intensive care units.

The goal of this paper is to present these problems of parent-medical staff interaction and to

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discuss one technique used in an attempt to resolve them. Opening up discussion between parents and medical personnel is not a unique endeavor. However, this report is intended to alert physicians to those factors that might not be freely spoken of by parents and yet underlie their concerns. The following case history will serve to keynote the discussion.

Report of a Case

Bobby T. was born weighing 1.02 kg, at a gestational age of 28 weeks, to Mrs. T. who was Gr III P II Ab O. The pregnancy was uncomplicated. Premature labor had led to the use of an alcohol infusion without result and birth occurred 36 hours later. Apgar scores were 1 and 0 at one and five minutes respectively. Resuscitation with endotracheal intubation, umbilical artery catheterization, and fluid and bicarbonate infusion restored the baby's pulse and color. Mechanically assisted respiration was required for the first 24 hours and oxygen for the next ten days. During this time the baby's course was complicated by hypoglycemia (necessitating treatment), apnea, abnormal spontaneous movements of arms and legs (described as seizures), a weight loss of 10 percent and possible sepsis. Cultures of blood, urine and cerebrospinal fluid were therefore made and treatment begun with antibiotics. Gavage feedings were started at 5 days of age. By 2 weeks of age his weight loss ceased, the abnormal movements of arms and legs had come to a halt, the cultures had returned negative and it was apparent that recovery was assured.

At this time it was also clear that the family was experiencing difficulty. Mrs. T. in fact had been alone through much of the labor and delivery, being visited only occasionally by a friend. Her husband, out of state on business at the time, had not been able to be present. Even after Bobby's birth he returned to the city only for a brief visit and then left again to resume his activity as before. Therefore, the burden of the early days was forced upon Mrs. T. without support from her family. Before her discharge she saw the baby once and then went home for a period of rest. During the baby's early crises, the family's interactions were entirely by telephone and then only once every three days. The mother did finally join her husband on his business trip. It became apparent later that the family's difficulties at this stage were a reflection of their concern and not an attempt to ignore the seriousness of the situation.

Because of its program involving premature infants at the University of California at Los Angeles, the Division of Child Development became involved after the baby entered his recovery phase. Initial contact with the family was made by a nursery social worker following their return to this city. There was great reluctance by the mother to visit the baby; illness was frequently cited as the reason. Mr. T. in fact saw the baby only at discharge, a situation created, he stated, by the demands of his occupation.

The initial goals of the physician and nurse from Child Development were to be supportive at this time not only of the family but also of the house staff and nurses caring for the infant. As the baby improved and did well, it was possible to reassure them and to point out the positive features of the baby's behavior. Mrs. T. was told that even though all her initial questions could not be answered, others recognized her concerns and would attempt to provide answers as they became known. At this time her anxiety peaked and questions about placing the baby in a "mental institution" were raised even though the baby had begun to thrive.

The first time Mrs. T. saw Bobby close-up and held him was six weeks after she herself had left the hospital. It took a good deal of encouragement to help her make the first overture toward him. On subsequent visits to the nursery, she brought someone who was to help care for him—it was her intention to allow her domestic servant to be the person who would care for the child primarily. This of course complicated the task of helping Mrs. T. make an attachment to her baby. As the public health nurse became more involved with the family a good deal of listening was required. At the same time strengths were looked for in both Bobby and Mrs. T. that could be pointed out to her. The special care needed for a premature infant was discussed without overemphasizing potential problems. The physician and nurse made themselves available to the family as needed in order to support their efforts and answer their questions.

On the day of discharge the physician-nurse team had the opportunity to see Mr. and Mrs. T. together. There appeared to be very little physical or emotional support from Mr. T., a fact confirmed by his wife in subsequent interviews. Mrs. T. took Bobby home alone that day and Mr. T.

went on to work. Mrs. T. was encouraged to call whenever necessary and it was agreed that the nurse would phone her the following day.

During that conversation the next day, Mrs. T. indicated that she had already taken on the role of primary provider of care. Actually, she and her servant alternately handled the night feedings. As she cared for Bobby it was possible for her to observe what his strengths were and she derived a good deal of pleasure from this.

The first few weeks that the baby was at home were without difficulty. He slept well and his feedings were normal. However, in the ensuing months his crying became more demanding and Mrs. T. found this very difficult to tolerate. Feelings of hostility surfaced, but because of her relationship to the physician-nurse team she was able to express this hostility openly with them. They in turn were able to appreciate the stresses with which she was dealing. As Bobby grew, it was apparent that his development was indeed normal both mentally and behaviorally. This was discussed with his mother and she was encouraged to proceed with plans to develop her own free time and do some of the things she enjoyed. In this way she was better able to tolerate the difficult times and to enjoy the pleasant times she and Bobby had together.

Results of formal testing of Bobby have shown no evidence of handicap: at four months of age the Gesell development quotient was 106, at 9 months it was 90. A cognitive examination at nine months of age based on the Piaget sensorimotor scheme was felt to give normal findings. With time the frequency of home visits by the nurse and appointments at the clinic with a pediatrician decreased in number as the family was able to assume more and more of the responsibility of observing Bobby's behavior and arriving at healthy techniques in managing his normal problems themselves.

It is recognized that this family has had difficulties and in all likelihood will continue to have them. It is possible that they will need more active intervention in the future, but the goal of allowing the baby to achieve full potential was realized. The attachment of the parents to their baby was aided at a time that was felt to be crucial to his development. Mrs. T., in fact, was able to see strengths in herself that she had not been aware of before. Also her ability to observe behaviors in her son and to appreciate his development grew remarkably.

Discussion

Using this case history as a model, it is possible to identify overlapping stages of parent-staff interactions. These indicate what parental concerns exist during the various periods of the infant's development. In order to present our goals some brief description of these phases is in order.

Acute Phase—This period immediately follows birth and encompasses the major events affecting an ill newborn infant. It is the time when there is realistic concern about survival. It is also the time when little may be explained to the mother.

The father, because of work, obligations to other children or other reasons, may not be available for discussion. The parents may not press the staff for information and as a result little exchange may occur. In the case of Bobby the family in fact chose not to be present at all. Their reluctance to visit, however, was actually a sign that they truly appreciated the seriousness of their baby's condition.

Recovery Phase—It has now become apparent that the baby will survive. However, the parents may not ask to be told what the baby has passed through. Conversely, the medical staff may not want to discuss those events in detail because they may not feel secure in relating them to outcome. In fact both sides may feel that a baby who has survived such serious events cannot possibly be normal. These worries may not be put in words by either side. Mrs. T.'s questions during this period about placement of the baby in a mental institution reflected her anxiety about these events.

Discharge Phase—Questions about the future remain but suddenly the potential burden of day-to-day care becomes a major factor. Preparations for feeding, dressing and bathing are made and discharge is contemplated. The impact of providing for a baby who nearly died but survived—and who may be presumed by the parents to be defective—is a major undertaking. Upon discharge the mother may be given an appointment to the Well Baby Clinic, to a city clinic or occasionally to the office of a private physician. In the former two situations, the family will be forced to adjust to health personnel with whom there has been no earlier contact.[12]

Postdischarge Phase—The full impact of providing care for the infant is suddenly upon the family, predominantly the mother. Frequent daily disruptions which are distressing in the normal

situation may be exaggerated out of proportion. To a parent, crying by the infant may represent defective behavior; spitting-up may bring back the earlier concerns in the nursery when so much effort was centered around the feedings. Quite often the family will begin to see the child as extremely vulnerable—a pattern that may be difficult to reverse in the months to come.[13]

Long-Term Follow-up Phase—With the continued support offered by a physician and a nurse, and the usual normal development of the infant, this period will find parental fears relaxing. However, it is not uncommon for feelings about the vulnerability of their child to persist for months and years. The physician and nurse will find it necessary not to demand an unrealistic resolution of all parental concerns but rather to hope to see gradual control over them develop.

The role of the physician and nurse who will care for the baby after discharge is guided by a single goal: to provide the most optimal circumstances in which the baby might thrive and develop to the fullest potential. The expression of this goal depends on the family and the type of concern it is experiencing. This leads us to a discussion of the role of the physician and nurse.

The Nurse's Role

A public health nurse skilled in the area of child development has a unique opportunity to provide true continuity of care. Parent-nurse interaction begins before discharge but becomes very important when the infant is at home. No other member of the health personnel group is in such a position to provide this help.

Within the nursery, such things as crying, startle responses and difficulties in feeding are handled casually by the house staff and an intensive care unit nurse. As a result the mother may truly not have the opportunity to clarify her questions about such patterns of behavior. At home she may question whether they represent abnormalities. The misinterpretation of normal crying is often made by parents. Until the family returns to the pediatrician for an initial examination of the infant, enough time may pass to allow for the creation of aberrant maternal responses and difficulty in the interaction between infant and mother.[14] This period, therefore, demands that attention from a trained observer be available early and that constructive intervention be applied to prevent the occurrence and persistence of these maladaptive patterns.

Initially then, these issues of behavior by the infant and what it represents can be discussed. That the infant has in fact developed can be shown; problem areas, be they behavioral such as crying or related to day-to-day management, can be given attention that takes into account the mother's ability and her perception of the difficulties, and the nurse's experience.

On subsequent clinic visits, the nurse can meet with the family along with the physician. Questions that they may find difficult to ask the physician can be encouraged openly by the nurse. With time, the frequency of nurse visits to the home may vary. In those situations where early problems are resolved comfortably, they will usually decrease.

The Physician's Role

During the initial stage of the acute postnatal events in the intensive care unit, a physician from the child development clinic may not be involved with the family, but by being present in the nursery it will be possible for him to discuss the significance of perinatal problems with house staff and their relationship to subsequent development. Because current reports strongly suggest that the intensive care provided for sick neonates is lowering morbidity, the child development physician will have the opportunity to encourage the continuation of care. It is important to emphasize that this support be directed not only to the house staff involved but also to the nursing personnel, who are usually in frequent contact with the parents.

As the condition of the baby improves, an initial approach to the family can be made. Questions about prognosis are often heard, but because of the nature of the situation many of these questions cannot be answered. It is also apparent that parents are not always asking for specific answers, but rather are seeking an opportunity to voice their anxieties. The physician, in turn, can show willingness to share these worries and to assure the family that as the answers become known they will be supplied. It is important to allow the parents to meet the public health or child development nurse at this time. In fact, the nurse's role becomes vital as discharge approaches. The physician aranges follow-up appointments and provides the family with a means to contact him should it be necessary.

Later as the baby matures, the answers to the parents' early questions will become available.

The unknown factors gradually will be dealt with. In those situations where handicapping conditions arise—either within the child or within the family—they can be handled appropriately by the physician and nurse because of their knowledge of the people involved.

Conclusions

In medicine, as elsewhere, it is uncommon to find a sequence of events fall into set patterns. Certainly the periods outlined here do not occur separately. Rather, there is great overlap; concerns over life and death may be expressed months after birth or the fear of brain damage may be present even within a few days of delivery. Our purpose in identifying specific phases is to encourage physicians and nurses to think about what the families of their patients may be considering and what may enter into their interactions with the medical staff. We have found that the presence in the nursery of personnel who are familiar and comfortable with the data on long-term outcome does not inhibit discussion between house staff and parents—but in fact promotes it. Further, the continuity provided by having the outpatient physician and nurse meet the family before discharge of the infant is important. It is to be hoped that in the future house staff might in fact be able to assume this role as they become more aware of the improving outcomes for patients cared for in nursery intensive care units.

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in memoriam

Bryan, Allen L., Point Loma. Died March 6, 1976 in Point Loma, aged 57. Graduate of Temple University School of Medicine, Philadelphia, 1943. Licensed in California in 1947. Dr. Bryan was a member of the San Diego County Medical Society.

Clark, Dorothy Velma (Dorothy Velma Clark Loveall), Los Angeles. Died March 4, 1976 in Los Angeles of complications of pneumonia, aged 64. Graduate of the Medical College of Virginia, Richmond, 1936. Licensed in California in 1940. Dr. Clark was a member of the Los Angeles County Medical Association.

Clemmer, Clarence V., Pasadena. Died June 13, 1975 of cerebrovascular accident, aged 89. Graduate of Hahnemann Medical School and Hospital of Philadelphia, 1910. Licensed in California in 1933. Dr. Clemmer was a retired member of the Los Angeles County Medical Association.

Fehlmann, Frederick H., San Diego. Died March 13, 1976, aged 64. Graduate of the University of Michigan Medical School, Ann Arbor, 1937. Licensed in California in 1937. Dr. Fehlmann was a member of the San Diego County Medical Society.

Forney, Robert L., Bakersfield. Died February 27, 1976 in Bakersfield of heart disease, aged 62. Graduate of the University of California Medical School, Berkeley-San Francisco, 1938. Licensed in California in 1939. Dr. Forney was a member of the Kern County Medical Society.

Grantham, David Marshall, Oakland. Died March 15, 1976, aged 68. Graduate of Northwestern University Medical School, Chicago, 1934. Licensed in California in 1934. Dr. Grantham was a retired member of the Alameda-Contra Costa Medical Association.

Hawkins, Ralph L., Palo Alto. Died March 28, 1976 in Palo Alto, aged 68. Graduate of Harvard Medical School, Boston, 1933. Licensed in California in 1940. Dr. Hawkins was a member of the Santa Clara County Medical Society.

Howell, Homer Preston, Oakland. Died March 5, 1976 in San Jose of malignant brain tumor, aged 65. Graduate of Northwestern University Medical School, Chicago, 1937. Licensed in California in 1944. Dr. Howell was a member of the Alameda-Contra Costa Medical Association.

Langer, Joseph B., San Bernardino. Died February 17, 1976 in San Bernardino, aged 73. Graduate of the University of Oregon Medical School, Portland, 1928. Licensed in California in 1928. Dr. Langer was a member of the San Bernardino County Medical Society.

Lauber, Donald Jack, Santa Ana. Died March 25, 1976 of heart disease, aged 49. Graduate of the University of California Medical School, Berkeley-San Francisco, 1954. Licensed in California in 1955. Dr. Lauber was a member of the Orange County Medical Association.

McCreery, William Brower, Atherton. Died March 9, 1976, aged 55. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1945. Licensed in Caliornia in 1946. Dr. McCreery was a member of the San Mateo County Medical Society.

Montgomery, Earl C., Moraga. Died May 20, 1975 of arteriosclerotic cardiovascular disease, aged 83. Graduate of the University of Nebraska College of Medicine, Omaha, 1917. Licensed in California in 1938. Dr. Montgomery was a retired member of the Alameda-Contra Costa Medical Association.

Okker, William X., Oakland. Died February 20, 1976 in Oakland of generalized peritonitis, aged 66. Graduate of the University of California Medical School, Berkeley-San Francisco, 1938. Licensed in California in 1938. Dr. Okker was a member of the Alameda-Contra Costa Medical Association.

Ream, George Douglas, Albany. Died February 28, 1976 in Kensington of cerebrovascular accident, aged 80. Graduate of the University of California Medical School, Berkeley-San Francisco, 1932. Licensed in California in 1932. Dr. Ream was a retired member of the Alameda-Contra Costa Medical Association.

Seitter, Paul F., Balboa Island. Died May 13, 1975, aged 65. Graduate of the University of Southern California School of Medicine, 1935. Licensed in California in 1935. Dr. Seitter was a member of the Los Angeles County Medical Association.

Trace, Robert J., Garden Grove. Died August 14, 1975, aged 49. Graduate of the University of Maryland School of Medicine, Baltimore, 1952. Licensed in California in 1957. Dr. Trace was a member of the Orange County Medical Association.

Turco, Evarist Angelo, San Jose. Died February 26, 1976 in San Jose, aged 86. Graduate of Regia Università di Torino, Facoltà di Medicina e Chirurgia, 1915. Licensed in California in 1924. Dr. Turco was a retired member of the Santa Clara County Medical Society.

Warren, John W., National City. Died February 26, 1976 in National City, aged 85. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1916. Licensed in California in 1916. Dr. Warren was a retired member of the San Diego County Medical Society.

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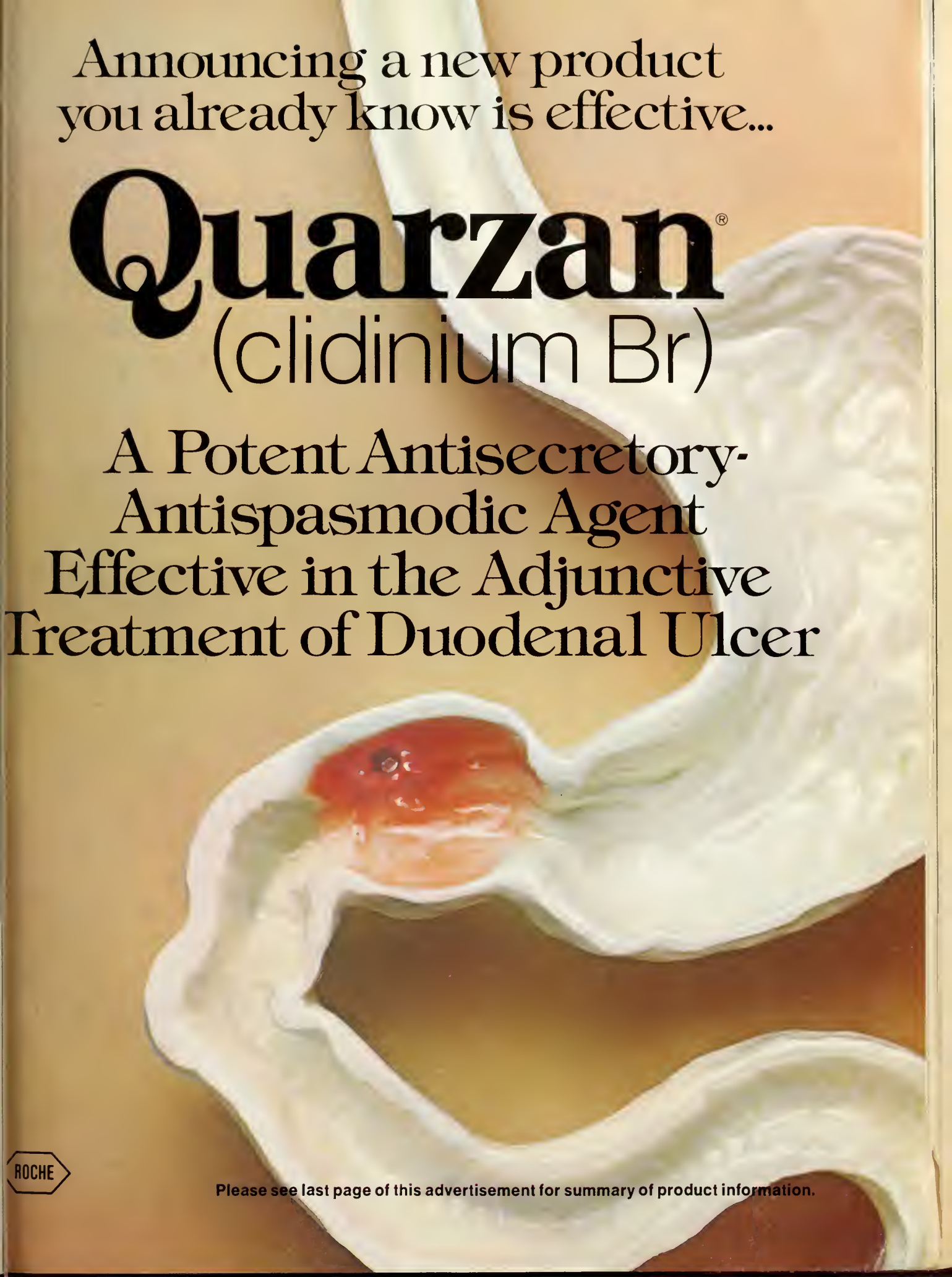

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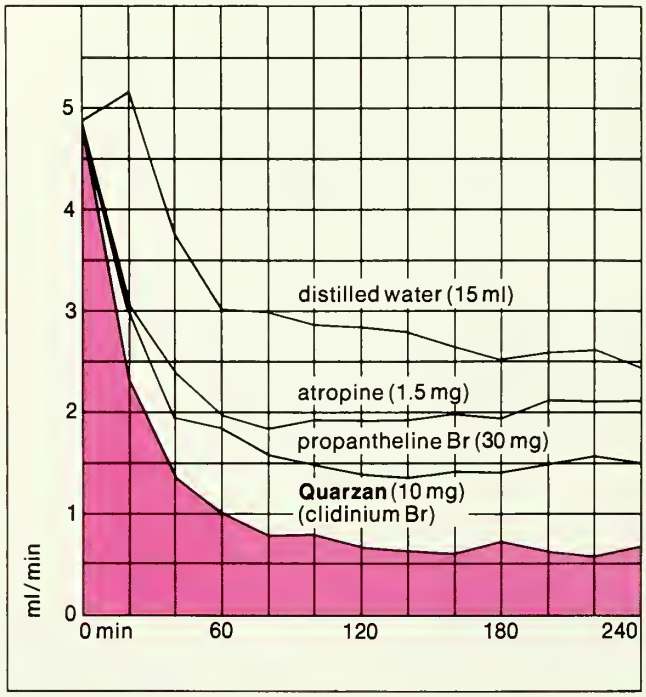

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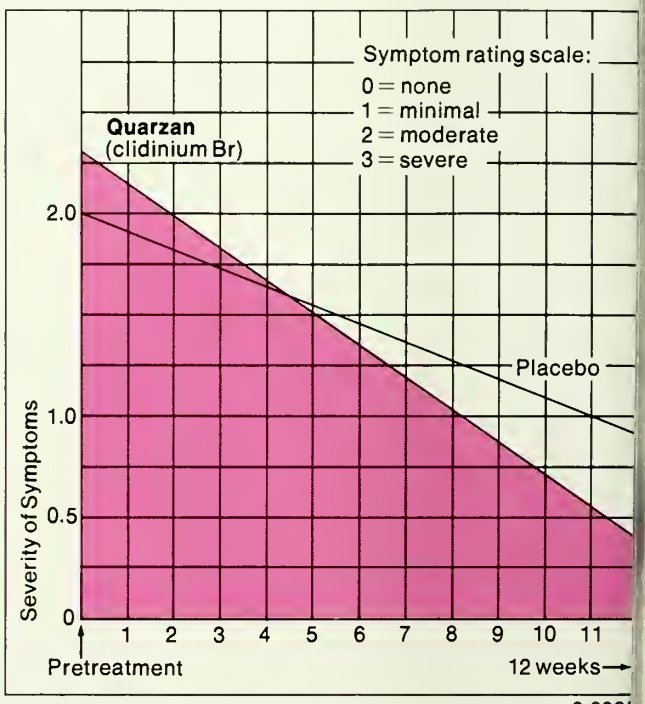

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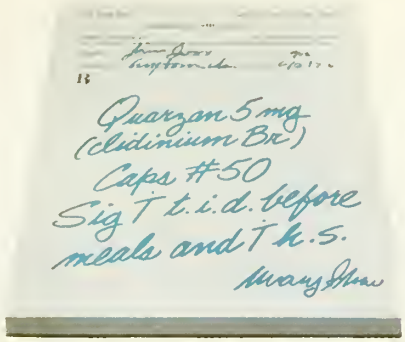

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Quarzan is contraindicated in patients with glaucoma, obstructive uropathy or known hypersensitivity to clidinium Br or other anticholinergic drugs. (See product information for complete list of contraindications.) For the aged and debilitated, one 2.5-mg capsule t.i.d. before meals is recommended.

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Quarzan®

(clidinium Br)

2.5 mg and 5 mg capsules

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Quarzan®
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(Continued from Page 26)

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(Continued on Page 38)

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IN GONORRHEA

INJECTION

Wycillin®

(STERILE PENICILLIN G PROCAINE SUSPENSION) WYETH

In **Gonorrhea,** the drug regimen of choice is aqueous penicillin G procaine. In uncomplicated cases, administration of 4.8 million units together with 1 gram oral probenecid, given just before injection, is recommended.

Indications: In treatment of moderately severe infections due to penicillin G-sensitive microorganisms sensitive to the low and persistent serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: When high sustained serum levels are required use aqueous penicillin G, IM or IV.

The following infection will usually respond to adequate dosages of intramuscular penicillin G procaine—*N. gonorrhoeae:* acute and chronic (without bacteremia).

For deep intramuscular injection only.

Contraindication: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well-documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents, e.g., pressor amines, antihistamines, and corticosteroids.

Immediate toxic reactions to procaine may occur in some individuals, particularly when a large single dose is administered in the treatment of gonorrhea (4.8 million units). These reactions may be manifested by mental disturbances, including anxiety, confusion, agitation, depression, weakness, seizures, hallucinations, combativeness, and expressed "fear of impending death". The reactions noted in carefully controlled studies occurred in approximately one in 500 patients treated for gonorrhea. Reactions are transient, lasting from 15-30 minutes.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 ml. of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparations should not be used. Antihistaminics appear beneficial in treatment of procaine reactions.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy, discontinue penicillin and take appropriate measures.

If allergic reaction occurs, withdraw penicillin unless in the opinion of the physician, the condition being treated is life threatening and amenable only to penicillin therapy.

When treating gonococcal infections with suspected primary or secondary syphilis, perform proper diagnostic procedures, including darkfield examinations. In all cases in which concomitant syphilis is suspected, perform monthly serological tests for at least four months.

Adverse Reactions: (Penicillin has significant index of sensitization) skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; serum sickness-like reactions, including chills, fever, edema, arthralgia and prostration. Severe and often fatal anaphylaxis has been reported. (See "Warnings.")

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Procaine toxicity manifestations have been reported (see "Warnings"). Procaine hypersensitivity reactions have not been reported with this drug.

Dosage and Administration: Administer only by *deep intramuscular injection,* in upper outer quadrant of buttock. In infants and small children, midlateral aspect of thigh may be preferable. When doses are repeated, vary injection site. Before injection, aspirate to be sure needle bevel is not in blood vessel. If blood appears, remove needle and inject in another site.

Although some isolates of *Neisseria gonorrhoeae* have decreased susceptibility to penicillin, this resistance is relative, not absolute, and penicillin in large doses remains the drug of choice. Physicians are cautioned not to use less than recommended doses.

Gonorrheal infections (uncomplicated)—Men or Women: 4.8 million units intramuscularly divided into at least two doses and injected at different sites at one visit, together with 1 gram of oral probenecid, given just before injection.

NOTE: Treatment of severe complications of gonorrhea should be individualized using large amounts of short-acting penicillin. Gonorrheal endocarditis should be treated intensively with aqueous penicillin G. Prophylactic or epidemiologic treatment for gonorrhea (male and female) is accomplished with same treatment schedules as for uncomplicated gonorrhea.

Retreatment: The National Center for Disease Control, Venereal Disease Branch, U.S. Dept. H.E.W. recommends:

Test cure procedures at approximately 7-14 days after therapy. In the male, a gram-stained smear is adequate if positive; otherwise, a culture specimen should be obtained from the anterior urethra. In the female, culture specimens should be obtained from both the endocervical and anal canal sites.

Retreatment in males is indicated if urethral discharge persists 3 or more days following initial therapy and smear or culture remains positive. Follow-up treatment consists of 4.8 million units aqueous penicillin G procaine, I.M. divided in 2 injection sites at single visit.

In uncomplicated gonorrhea in the female, retreatment is indicated if follow-up cervical or rectal cultures remain positive for *N. gonorrhoeae.* Follow-up treatment consists of 4.8 million units aqueous penicillin G procaine daily on 2 successive days.

Syphilis: all gonorrhea patients should have a serologic test for syphilis at the time of diagnosis. Patients with gonorrhea who also have syphilis should be given additional treatment appropriate to the stage of syphilis.

Composition: Each disposable syringe 2,400,000 units (4-ml. size) contains penicillin G procaine in a stabilized aqueous suspension with sodium citrate buffer, and as w/v approximately 0.5% lecithin, 0.5% carboxymethylcellulose, 0.5% povidone, 0.1% methylparaben, and 0.01% propylparaben. The multiple-dose 10-ml. vial contains per ml. 300,000 units penicillin G procaine in a stabilized aqueous suspension with sodium citrate buffer and approximately 7 mg. lecithin, 2 mg. carboxymethylcellulose, 3 mg. povidone, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben, and 0.14 mg. propylparaben.

Five are graduating with honors. How many with VD?

On the average, you can figure the incidence of VD among teenagers at about 900 per 100,000 population.* And growing.

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In the long run, a populace educated to the risks and prevention of VD is probably the best answer to the problem. Meanwhile, though, adequate doses of the recommended types of penicillin remain a formidable weapon.

IN SYPHILIS
NJECTION
Bicillin® L-A
STERILE PENICILLIN G BENZATHINE SUSPENSION) WYETH

Syphilis is preferably treated with penicillin G benzathine, which is also the drug of choice for prophylaxis after exposure. Administration of 2.4 million units (1.2 million in each buttock) usually cures most cases of primary, secondary and latent syphilis with negative spinal fluid.

Indications: In treatment of infections due to penicillin-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular penicillin G benzathine. — Venereal infections: Syphilis, yaws, bejel and pinta.

For deep intramuscular injection only.

Contraindication: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens.

Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms including fungi. Take appropriate measures should superinfection occur.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness-like reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high doses of parenteral penicillin.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Dosage and Administration: Venereal infections —

Syphilis — Primary, secondary and latent — 2.4 million units (1 dose).

Late (tertiary and neurosyphilis) — 2.4 million units at 7 day intervals for three doses.

Congenital — under 2 years of age, 50,000 units/Kg. body weight; ages 2-12 years, adjust dosage based on adult dosage schedule.

(Shake multiple-dose vial vigorously before withdrawing the desired dose.) Administer by **deep intramuscular injection** in the upper outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site. Before injecting the dose, aspirate to be sure needle bevel is not in a blood vessel. If blood appears, remove the needle and inject in another site.

Composition: Units penicillin G benzathine (as active ingredient): 2,400,000 units in 4-ml. single dose disposable syringe. Each disposable syringe also contains in aqueous suspension with sodium citrate buffer, as w/v approximately 0.5% lecithin, 0.6% carboxymethylcellulose, 0.6% povidone, 0.1% methylparaben, and 0.01% propylparaben. 300,000 units per ml. — 10-ml. multi-dose vial. Each ml. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. povidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben, and 0.14 mg. propylparaben.

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Dept. of Health, Education, and Welfare: VD Fact Sheet 1972. Publication No. (HSM) 73-8195

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the weight of ethical opinion:

Few would disagree that the effectiveness and safety of any therapeutic agent or device must be determined through clinical research.

But now the *practice* of clinical research is under appraisal by Congress, the press and the general public. Who shall administer it? On whom are the products to be tested? Under what circumstances? And how shall results be evaluated and utilized?

The Pharmaceutical Manufacturers Association represents firms that are significantly engaged in the discovery and development of new medicines, medical devices and diagnostic products. Clinical research is essential to their efforts. Consequently, PMA formulated positions which it submitted on July 11, 1975, to the Subcommittee on Health of the Senate Labor and Public Welfare Committee, as its official policy recommendations. Here are the essentials of PMA's current thinking in this vital area.

1. PMA supports the mandate and mission of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and offers to establish a special committee composed of experts of appropriate disciplines familiar with the industry's research methodology to volunteer its service to the Commission.

2. PMA supports the formation of an independent, expert, broadly based and representative panel to assess the current state of drug innovation and the impact upon it of existing laws, regulations and procedures.

3. When FDA proposes regulations, it should prepare and publish in the *Federal Register* a detailed statement assessing the impact of those regulations on drug and device innovation.

4. PMA proposes that an appropriately qualified medical organization be encouraged to undertake a comprehensive study of the optimum roles and responsibilities of the sponsor and physician when company-sponsored clinical research is performed by independent clinical investigators.

5. PMA recognizes that the physician-investigator has, and should have, the ultimate responsibility for deciding the substance and form of the informed consent to be obtained. However, PMA recommends that the sponsor of the experiment aid the investigator in discharging this important responsibility by providing (1) a document detailing the investigator's responsibilities under FDA regulations with regard to patient consent, and (2) a written description of the relevant facts about the investigational item to be studied, in comprehensible lay language.

6. In the case of children, the sponsor must require that informed consent be obtained from a legally appropriate representative of the participant. Voluntary consent of an older child, who may be capable of understanding, in addition to that of a parent, guardian or other legally responsible person, is advisable. Safety of the drug or device shall have been assessed in adult populations prior to use in children.

7. PMA endorses the general principle that, in the case of the mentally infirm, consent should be sought from both an understanding subject and from a parent or guardian, or in their absence, another legally responsible person.

8. Pharmaceutical manufacturers sponsoring investigations in prisons must take all reasonable care to assure that the facilities and personnel used in the conduct of the investigations are suitable for the protection of participants, and for the avoidance of coercion, with a respect for basic humanitarian principles.

9. Sponsors intending to conduct non-therapeutic clinical trials through the participation of employee volunteers should expand the membership and scope of its existing Medical Research Committee, or establish such an internal Medical Research Committee, with responsibility to approve the consent forms of all volunteers, designs, protocols and the scope of the trial. The Committee should also bear responsibility to ensure full compliance with all procedures intended to protect employee volunteers' rights.

10. Where the sponsor obtains medical information or data on individuals, it shall be accorded the same confidential status as provided in codes of ethics governing health care professionals.

11. PMA and its member firms accept responsibility to aid and encourage appropriate follow-up of human subjects who have received investigational products that cause latent toxicity in animals or, during their use in clinical investigation, are found to cause unexpected and serious adverse effects.

12. PMA supports the exploration and development by its member companies of more systematic surveillance procedures for newly marketed products.

13. When a pharmaceutical manufacturer concludes, on the basis of early clinical trials of a basic new agent, that a new drug application is likely to be submitted, a proposed development plan accompanied by a summary of existing data, would be submitted to the FDA. Following a review of this submission, the FDA, and its Advisory Committee where appropriate, would meet with the sponsor to discuss the development plan. No *formal* FDA approval should be required at this stage. Rather, the emphasis should be on identification of potential problems and questions for the sponsor's further study and resolution as the program develops.

The PMA believes that health professionals as well as the public at large should be made aware of these 13 points in its Policy on Clinical Research. For these recommendations envisage constructive, cooperative action by industry, research institutions, the health professions and government to encourage creative and workable responses to issues involved in the clinical investigation of new products.

P·M·A

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W.
Washington, D. C. 20005

(Continued from Page 31)

PHYSICIANS WANTED

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ORTHOPEDIST: Board certified or board eligible, for large multispecialty group. Department currently consists of seven orthopedists. Department and area expanding. Edward H. Start, MD, Chief of Orthopedics, The Permanente Clinic, 5055 North Greeley Ave., Portland, Oregon 97217.

PATHOLOGISTS: The Department of Pathology at UCLA is willing to consider applications for appointment to the Clinical Staff on a volunteer basis. Applicants should have expertise in teaching and an interest in participating in the instructional program for the Second Year Medical and Dental Students as well as Interns and Residents of the department. UCLA is an Equal Opportunity/Affirmative Action Employer. Send Curriculum Vitae to J. L. Van Lancker, MD, De? partment of Patrology, University of California, Los Angeles, Los Angeles, CA 90024.

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WANTED: Pediatrician and Family Practitioners by an eight-man group in Northeastern Wisconsin. Marinette has a population of 13,000 and its sister-city Menominee, Michigan has 12,000. Located on the beautiful waters of Green Bay, there are abundant recreational opportunities, excellent schools and modern hospital facilities. $40,000 salary first year, full corporate status second year. All fringes, including malpractice insurance, paid by clinic. Contact: Gerard De Bruin, Business Manager, Boren Clinic, 1510 Main St., Marinette, Wis. 54143.

(Continued on Page 40)

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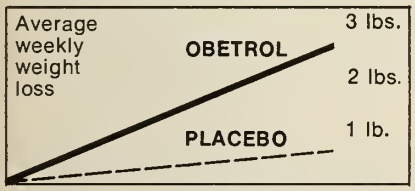

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Actions: Amphetamines are sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. The anorectic effect diminishes after a few weeks.

Indications: Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. For patients in whom obesity is refractory to other measures.

Contraindications: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncracy to the sympathomimetic amines. • Agitated states. • Patients with a history of drug abuse. • During or within 14 days following the administration of monoamine oxidase inhibitors, hypertensive crises may result.

Warnings: Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

Precautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen. Amphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Adverse Reactions: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic:* Urticaria. *Endocrine:* Impotence, changes in libido.

Dosage and Administration: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening medication should be avoided because of the resulting insomnia.

1. Narcolepsy: Usual dose 5 to 60 milligrams per day in divided doses.
2. Minimal brain dysfunction:
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   b. Children from 3 to 5 years of age: 2.5 milligrams daily, raised in increments of 2.5 milligrams at weekly intervals until optimal response is obtained.
   c. Children 6 years of age and older, 5 milligrams, once or twice daily, increased in increments of 5 milligrams at weekly intervals. Only in rare cases will it be necessary to exceed a total of 40 milligrams per day.
3. Obesity: Usual adult dose 5 to 30 milligrams per day in divided doses.

Overdosage: Manifestations of acute overdosage with amphetamines include restlessness, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.

Management of acute amphetamine intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations in this regard.

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January 1973

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Two positions available: 1-Director, 1-Staff Physician. Located in South Central Minnesota; on Campus enrollment of 10,000 students; metropolitan area of 50,000; current Minnesota license necessary. Salary competitive, five-day work week, liberal vacation, and fringe benefits. **Contact KAREN DELESHA, Administrative Director, Student Health Service, Mankato, Minnesota 56001; phone (507) 389-2726.** Equal Opportunity/Affirmative Action Employer.

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SEEKING BOARD CERTIFIED OR QUALIFIED INTERNIST, preferably with subspecialty in allergy or gastroenterology, to associate with two established internists with subspecialties in cardiology and pulmonary diseases. New office building and facilities with unlimited land available for expansion across from a major hospital. Rapidly growing county seat-university-community college town on central coast of California; population 40,000 with 150,000 in area and several State institutions. Financial arrangements open and negotiable, eventual partnership desired. Completely equipped office includes lab, x-ray. Excellent fringe benefits and supporting staff. Beautiful multifaceted recreational and geographic area; good schools and churches. Send curriculum vitae to Box Number 9464, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

MULTI-SPECIALTY CLINIC openings in South Central Kansas for general internist and general surgeon. Malpractice coverage no problem. Group rates paid by clinic. Our patients appreciate their physicians. If interested call: Area Code (316) 221-3200, collect. Ask for J. L. Mount, Clinic Administrator; or send résumé to: Snyder Clinic Association, P.O. Box 544, Winfield, Kansas 67156.

DEPARTMENT OF PEDIATRICS, UNIVERSITY OF CALIFORNIA at Los Angeles, School of Medicine, seeks a Chairman of the Department of Pediatrics at Kern Medical Center, its associated program in Bakersfield, California; Board Certification essential; salary competitive, full medical liability coverage. **Staff Pediatrician** position also available. Interested candidates should direct inquiries or submit credentials (including curriculum vitae) to Donald F. Brayton, MD, Medical Director, Kern Medical Center, 1830 Flower St., Bakersfield, CA 93305. Both the UCLA School of Medicine and Kern Medical Center are equal opportunity employers.

(Continued from Page 38)

PHYSICIANS WANTED

REASONABLE MALPRACTICE is still available in Colorado. GP or FP physician needed for rural community. Clinic provided advacent to well equipped modern hospital. We are in urgent need, so willing to discuss any type of arrangement. Contact Gary Thompson, Southeast Colorado Hospital, Springfield, Colorado 81073. Phone (303) 523-4501.

THE DEPARTMENT OF ANESTHESIOLOGY, UCLA SCHOOL OF MEDICINE, seeks a staff anesthesiologist for the Department of Anesthesiology at Kern Medical Center, its affiliate in Bakersfield, California. Board certification preferred, eligibility essential. Salary competitive, full medical liability coverage. Interested candidates should direct inquiries or submit credentials (including curriculum vitae) to Donald F. Brayton, MD, Medical Director, Kern Medical Center, 1830 Flower St., Bakersfield, CA 93305; telephone (805) 323-7651. Both the University of California and Kern Medical Center are equal opportunity employers.

ORTHOPEDIC SURGEON (ACADEMIC), to establish a teaching service in a university affiliated VA Hospital. Board certification in orthopedic surgery necessary. Send curriculum vitae and references to Veterans Administration Hospital; 510 E. Stoner; Shreveport, LA 71130.

WANTED—G.P. or F.P. to join me in a new clinic adjacent to a new full service hospital; group of one young G.P. and nurse practitioner here, making a nice work load. Excellent recreational area in Idaho; with good income potential. Malad Valley Clinic, Box 212, Malad, Idaho 83252.

CALIFORNIA—PEDIATRICIAN committed to concept of Ambulatory Pediatrics as a specialty. Challenge: Develop, institute and teach care that addresses unmet medical and emotional needs of everyday children and their families. Students: Pediatric and Family Practice house staff, medical students and pediatric nurse practitioners. Training: Preferably Child Development, Ambulatory Pediatrics, or MPH. Facility: Large pediatric outpatient department of UCSF affiliated medical center. Good salary. Professional liability insurance paid. Write: James McKenna, MD, Valley Medical Center, 445 South Cedar Ave., Fresno, CA 93702.

CALIFORNIA — HEMATOLOGIST-ONCOLOGIST. University-affiliated hospital in delightful California city is seeking an academically oriented hematologist-oncologist to head a Division of Hematology-Oncology and teach excellent resident staff. Geographic full-time. Professional liability insurance paid. Equal Opportunity Employer. Send curriculum vitae in first letter to: Jerome S. Harris, MD, Director of Medical Affairs, Valley Medical Center of Fresno, 445 So. Cedar, Fresno, CA 93702.

CALIFORNIA—ASSISTANT CHIEF OF FAMILY PRACTICE. University affiliated hospital in delightful California city is seeking an academically oriented family practitioner to assist Chief of Family Practice in thriving, innovative residency program. Geographic full-time. Professional liability insurance paid. Equal Opportunity Employer. Send curriculum vitae in first letter to: Jerome S. Harris, MD, Director of Medical Affairs, Valley Medical Center of Fresno, 445 So. Cedar, Fresno, CA 93702.

CALIFORNIA—NEPHROLOGIST. University-affiliated hospital in delightful California city is seeking an academically oriented nephrologist to head an active Nephrology Division of Department of Medicine. Excellent resident staff. Geographic full-time. Professional liability insurance paid. Send curriculum vitae in first letter to: Jerome S. Harris, MD, Director of Medical Affairs, Valley Medical Center of Fresno, 445 So. Cedar, Fresno, CA 93702.

WASHINGTON, OLYMPIA: Full-time Emergency Physician wanted. Requirements: Completed Emergency Medicine residency or minimum 3 year emergency medicine experience plus Washington State license and ACEP membership. Position open June 15, 1976 or earlier. Send curriculum vitae in first letter to P. H. Tonning, MD, St. Peter Hospital, 413 North Lilly Road, Olympia, Washington 98506; Phone: (206) 491-9480, Ext. 264 (Drs. Tonning or Urmanski, Tuesday-Friday).

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PHYSICIANS WANTED

EMERGENCY PHYSICIAN positions available with multi-hospital group in eastern Oregon. One hospital 50 minutes from Boise, Idaho; 2½ hours from Sun Valley. Other hospital 3 hours South of Yakima; 3 hours from skiing at Bend. Fee-for-service. Paid malpractice. No accounting, billing or personnel problems. Contact: Administrator, Emergency Physicians, 897 MacArthur Blvd., San Leandro, CA 94577.

SITUATIONS WANTED

ANESTHESIA FREE-LANCE service for office, clinic and hospital surgery. Our equipment on demand—at no cost. Call (213) 393-4267 or write: Associated Anesthesia Services, P.O. Box 1102, Santa Monica, CA 90406.

RHEUMATOLOGIST, 29, ABIM, completing 2 year fellowship, seeks group, associate, or hospital based practice, available fall, 1976. California licensed. Box No. 9470, Western Journal of Medicine, San Francisco, CA 94103.

EXPERIENCED LAB SUPERVISOR AND MICROBIOLOGIST wishes to set up basic, practical medical lab into medical complex. Warren Hillman, M.T., 2801 N. Bristol, #5, Santa Ana, CA 92706; (714) 543-4695.

PRACTICES FOR SALE

IDEAL CALIFORNIA CLIMATE to raise children—20-year established Pediatric practice in the San Francisco East Bay area for modest sale or reasonable lease—1975 gross over $120,000; net over $80,000—available immediately—5 bedroom home available, good schools, climate, churches, colleges, close to the East Bay's largest shopping complex, 5 local hospitals and Children's Hospital of Northern California within easy driving distance. Contact Box 9466 immediately. The Western Journal of Medicine, 731 Market St., S. F., CA 94103.

BUSY OPHTHALMOLOGY PRACTICE in handsome, growing, California college town. Excellent relationships wth fellow ophthalmologists. Top medical and surgical modalities available in office and hospitals. Fine family situation with superb recreational opportunities. Write Box No. 9467, Western Journal of Medicine, 731 Market St., S. F., CA 94103.

SAN FRANCISCO — UNIQUE OPPORTUNITY: Broad based family practice. Currently no OB or SURGEON. Busy and lucrative. Will introduce. Terms. Phone (415) 648-7360.

OFFICES FOR RENT OR LEASE

FOR RENT: The newest end largest professionel building in the South Sen Diego community of Imperiel Beach, suites eveilable cen be customized to suit tenant. This is excellent opportunity for pediatrics, gynecology, dermatology, ophthalmology, general surgery, general practice, internal medicine and psychiatry. Photos end particulars avellable upon request from John E. Geis, DDS, 1340 Coronedo Ave., Suite 201, Imperial Beach, CA 92032; office (714) 424-3931.

LARGE OFFICE for group, 2,400 sq. ft., x-ray and laboratory. Close to hospital, well designed. B. Berger, MD, Pinole, CA; (415) 758-2511.

MEDICAL SUITE AVAILABLE in the Foothill Medical Building, 21297 Foothill Blvd., Hayward, CA 94541. It consists of 850 sq. ft., 3 treetment rooms, waiting room, nurses station and private doctor's office. The building has an x-ray and medical laboratory, and a pharmacy. It is currently occupied by Family Practice Physicians predominantly. For information call (415) 582-6942.

FOR LEASE: Large office Ideal for small group located in Lawndale, California. Near Hewthorne Community Hospital end Gardena Memorial. Contact **Allen Hooper, MD, 1200 N. Stete St. P.O. Box 313, Los Angeles, CA 90033; Phone (213) 226-6675.**

CUSTOM BUILD OFFICE

CITRUS HEIGHTS, CA: Will Custom build office on beautiful lot next to existing medical complex. Starting loan and reduced rent available. R. Swisher, MD, 7618 Auburn Blvd., Citrus Heights, CA 95610.

FOR LEASE

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TRANSLATORS

JAPANESE/RUSSIAN—and other langueges, urgently needed for freelance assignments. Applicants should have advanced degrees or eq. experience with medical and technical texts. Please send prof. résumé to SCITRAN, Box 5456, Santa Barbara, CA 93108.

MEDICAL EQUIPMENT

FOR SALE: General Electric/Kermath Pneumoencephalographic Chair with Tomographic Carriage; Original Cost $10,000; Never Used—Best Offer; Contact: Arthur Gross, Children's Hospital Medical Center, 51st and Grove Sts., Oakland, CA 94609.

Beautiful two bedroom condominium in lovely Carmel Valley. Short walk to Quail Lodge and Carmel Valley Golf and Country Club. Access to 18 hole golf course and tennis courts. $1,200/month. For further information, call M. Johnson, (408) 659-2039 after 5 p.m.

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

RECENT ADVANCES IN OPHTHALMOLOGY—Number 5—Edited by P. D. Trevor-Roper, MD, FRCS, DOMS, Consultant Ophthalmic Surgeon, Westminister Hospital, Moorfields Eye Hospital and King Edward VII Hospital for Officers, London. Churchill Livingstone, Medical Division of Longman, Inc., 72 Fifth Avenue, New York City (10011), 1975. 319 pages, $30.00.

SLEEP—The Gentle Tyrant—Wilse B. Webb, PhD, Graduate Research Professor of Psychology, University of Florida. Prentice-Hall, Inc., Englewood Cliffs, NJ (07632), 1975. 192 pages, $7.95 cloth, $3.95 paperback.

STRESS FRACTURES—Michael Devas, FRCS, Consultant Orthopaedic Surgeon, Hastings Research Assistant to the Orthopaedic Department, The Middlesex Hospital, London. Churchill Livingstone, Medical Division of Longman, Inc., 72 Fifth Avenue, New York City (10011), 1975. 240 pages, $45.00.

A STUDY OF THE BIOLOGICAL SCIENCES IN RELATION TO NURSING—Kathleen J. W. Wilson, PHD, B Sc, RGN, SCM, RNT, Senior Research Fellow University of Birmingham and Nursing Research Liaison Officer, West Midlands Region. Churchill Livingstone, Medical Division, Longman Inc., 72 Fifth Avenue, New York City (10011), 1976. 166 pages, $9.75.

A TEXTBOOK FOR MEDICAL ASSISTANTS—Third Edition—M. Murray Lawton, MD, Administrator of the Berkley School, Director, In-Service Training, Berkley East Hospital, Santa Monica, California; and Donald F. Foy, BS, MS, MPH, Director, Management Services Division, American Medical Association, Chicago. The C. V. Mosby Company, Publishers, 3301 Washington Boulevard, St. Louis (63103), 1975. 469 pages, with 243 illustrations, $10.95.

THE VITAMIN C COOKBOOK—Cory Servaas, MD, and Walter Mathews, with introduction by Linus Pauling, PH D, Nobel Prize Winner and Professor of Chemistry, Stanford University. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1975. 154 pages, $6.95.

THE WALNUT CREEK CONTRACEPTIVE DRUG STUDY—A Prospective Study of the Side Effects of Oral Contraceptives—Volume 1—Edited by Savitri Ramcharan, MD, PhD, Research Director, Contraceptive Drug Study, Kaiser-Permanente Medical Center, Walnut Creek, California. U.S. Public Health Service, DHEW Publication No. (NIH) 74-562, 1975. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC (20402), $6.05, Stock Number 1746-00021.

WEBSTER'S MEDICAL SPELLER—G. & C. Merriam Company, 47 Federal Street, Springfield, Mass. (01101), 1975. 388 pages, $3.95.

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CONTINUING MEDICAL EDUCATION

WEEKEND COURSES

IN LOS ANGELES AND SAN FRANCISCO BAY AREA

Except where noted courses are given at the Holiday Inn, Hollywood (Highland and Hollywood Boulevard)

ERLE E. PEACOCK, MD — **JULY 17-18**
Professor of Surgery, University of Arizona
Modern Surgical Practice for Family Physicians
(Intensive Instruction in Diagnosis and Surgical Technique)

ZYGMUNT PIOTROWSKI, PhD — **JULY 24-25**
Professor Emeritus of Psychology, Jefferson Medical College
Diagnosis and Prognosis of Depression and Anxiety

MATTHEW BLOCK, PhD, MD — **JULY 31-AUGUST 1**
Professor of Medicine, University of Colorado
Blood Diseases: Current Practice

JOSEPH FINNEY, PhD, MD — **AUGUST 7-8**
Professor of Education, University of Kentucky
Modern Diagnosis of Emotional Conditions
By Interview, Tests, and Computer. (To assess risks of addiction, suicide, etc. and likelihood that bodily complaints are psychological.)

GEORGE DE VOS, PhD — **AUGUST 14-15**
Professor of Anthropology, University of California, Berkeley
Diagnosis Across Racial-Cultural Bounds
(Including His Testimony in the Sirhan Case)

ALBERT ELLIS, PhD — **OCTOBER 11-12**
Institute for Advanced Study in Rational Psychotherapy, New York. **Given in San Francisco.**
Rational Sex Therapy
First Day: Brief Successful Rational Counseling of Medical Patients
Second Day: Techniques of Sex Therapy; Ethics of Sex Therapy

RALPH SLOVENKO, PhD, LLB — **date not set**
Professor of Law and Psychiatry, Wayne State University
Mental Health and The Law

ANYONE ATTENDING ANY COURSE IS WELCOME TO BRING CLINICAL CASE MATERIALS FOR DISCUSSION
Fees: Two-day course $100. Either day alone $60. Six hours/day. Twenty percent reduction to interns and residents and to persons with less than a doctoral degree.

Dr. Piotrowski will also give two five day courses, in the Los Angeles Area, for Psychiatrists. July 19-23 Scientific Rorschach Testing. July 26-30 A Scientific System of Dream Analysis. Fee $200 for either course, $350 for both.

AIHS will receive proposals from nationally-known physicians and related professionals who would like to give other courses.

(WJM)

TO: AIHS Registrar, 2021 Grismer #14, Burbank, CA 91504

Enclosed is a check for my fee. Please enroll me in the course

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COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: For a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education, please write to the above address.

ALCOHOLISM AND DRUG ABUSE

May 21-23—**Alcoholism and Drug Abuse.** UCSF. Friday-Sunday.

May 27-29—**National Conference on Radiation Oncology.** American Cancer Society at Hilton Hotel, San Francisco. Thursday-Saturday. Contact: S. L. Arje, MD, ACS, 777 3rd Ave., New York 10017.

CANCER

June 21-25—**Head and Neck Oncology.** UCLA. Monday-Friday.

MEDICINE

May 18—**Seminars in Nephrology.** USC. Tuesday.

May 21—**Diagnosis and Treatment of Hypertension.** PMC. Friday.

May 22-23—**Dermatology/Hematology.** UCLA. Saturday-Sunday.

June 4-5—**Pediatric Neurosciences Symposium—2nd Annual.** Dominican Neurological Institute at Convention Center, Holiday Inn, Santa Cruz. Friday-Saturday. 10 hrs. Contact: G. A. Magid, MD, Dominican Hospital, 1555 Soquel Dr., Santa Cruz 95060. (408) 476-0220.

June 5—**Pulmonary Artery Catheters and Ventilators.** PMC. Saturday. $250.

June 8-11—**Core Curriculum in Echocardiography: New Developments in Cardiac Ultrasound.** American College of Cardiology, San Diego County Heart Assn., UCSD, Naval Regional Medical Center, at Town and Country Hotel, San Diego. Tuesday-Friday. Contact: ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

June 18—**Allergy for the Busy Office Practice.** PMC. Friday.

June 23-25—**The Endocrine Society—58th Annual Meeting.** Hilton Hotel, San Francisco. Wednesday-Friday. Contact: The Endocrine Society Annual Meeting Office, 9650 Rockville Pike, Bethesda, Md. 20014.

June 29-July 2—**Interpretative Enzymology.** UCSD. Tuesday-Friday.

July 12-15—**2nd International Symposium on Psoriasis.** STAN. Monday-Thursday.

August 3—**Seminars in Nephrology.** USC. Tuesday.

August 25-27—**Cardiology Today: For the Physician in Clinical Practice.** Mt. Zion Hospital and Medical Center, Univ. of Pittsburgh School of Medicine, under auspices of the Council on Clinical Cardiology of American Heart Assn., at St. Francis Hotel, San Francisco. Wednesday-Friday. Contact: Cont. Education, Mt. Zion Hospital & Medical Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2401.

August 29-September 4—**In-Depth Nephrology Board Review Course.** Cedars-Sinai Medical Center at Beverly Hilton Hotel, Los Angeles. One week. 60 hrs. $300. Contact: Andrew Lewin, MD, Renal Hypertension, Cedars-Sinai Medical Center, P.O. Box 48750, Los Angeles 90048. (213) 855-4671.

OBSTETRICS AND GYNECOLOGY

May 15-16—**Gyn-Urology.** USC at Biltmore Hotel, Santa Barbara. Saturday-Sunday.

July 17-19—**Basic Laparoscopy: Current Principles and Practice.** UCSD. Saturday-Monday.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

PEDIATRICS

May 21-23—**American Academy of Pediatrics, California Chapter I, District IX.** Ahwahnee Hotel, Yosemite. Friday-Sunday. Contact: Melvin H. Schwartz, MD, 2219 Santa Clara Ave., Alameda 94501.

May 23-26—**Recent Advances in Pediatric Neurology.** UCLA at Ahwahnee Hotel, Yosemite. Sunday-Wednesday.

June 4-5—**Pediatric Neurosciences Symposium—2nd Annual.** See Medicine, June 4-5.

June 11—**Conference on Prematurity—15th Annual.** STAN. Friday.

June 11-12—**Depression in Children.** See Psychiatry, June 11-12.

PSYCHIATRY

May 16-19—**Biofeedback—3rd Annual Program.** UCLA at Ahwahnee Hotel, Yosemite. Sunday-Wednesday.

June 11-12—**Depression in Children.** UCD at Marriott Inn, Berkeley. Friday-Saturday.

June 11-12—**Human Behavior.** USC. Friday-Saturday.

June 18-19—**Clinical Biofeedback in Medicine: Psychiatry and Pyschology.** UCD at Claremont Inn, Berkeley. Friday-Saturday.

June 19-20—**Advanced Psychotherapeutic Techniques.** UCLA. Saturday-Sunday.

June 23—**The Suicidal Patient: Recognition and Evaluation.** See Of Interest To All, June 23.

RADIOLOGY AND PATHOLOGY

May 21-23—**California Radiological Society—Annual Meeting.** Del Monte Hyatt House, Monterey. Friday-Sunday. Contact: CRS, 1225 8th St., Suite 590, Sacramento 95814. (916) 446-2028.

June 11-13—**American Association of Neuropathologists—Annual Meeting.** Hyatt Regency, San Francisco. Friday-Sunday. Contact: Richard L. Davis, MD, LAC-USC Medical Center, 1200 N. State St., Los Angeles 90033. (213) 226-7123.

June 20-26—**Pathology of the Lung.** UCSD. One week.

SURGERY AND ANESTHESIOLOGY

May 15-16—**Gynecology-Urology.** See Obstetrics and Gynecology, May 15-16.

May 16-28—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. 100 hrs. $1,200 for otolaryngologists; $900 for residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

May 20-21—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

May 20-22—**Neurosurgery—6th Annual Postgraduate Course.** UCSF at St. Francis Hotel, San Francisco. Thursday-Saturday.

May 23-26—**Recent Advances in Pediatric Neurology.** See Pediatrics, May 23-26.

June 3-5—**Highlights of Ophthalmology.** PMC at Golden Gateway Holiday Inn, San Francisco. Thursday-Saturday.

June 4—**Phacoemulsification Surgery Course.** Jules Stein Eye Institute, Los Angeles. Friday. $250. Contact: Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles.

June 4-5—**Intraocular Lens Implantation.** Santa Monica Hospital Medical Center, Santa Monica. Friday-Saturday. 16 hrs. $600. Contact: Jeanne Harris, Charlie Ruggles Ophthalmology Dept., Santa Monica Hospital Medical Center, 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

June 5—**Sports Medicine.** See Of Interest To All, June 5.

June 10-12—**Glaucoma.** UCSF at Quail Lodge, Monterey. Thursday-Saturday.

June 12-13—**Modern Laryngoscopy and Bronchoesophagoscopy: A Theoretical and Practical Course.** UCLA. Saturday-Sunday. $300; $150, residents. Contact: Paul H. Ward, MD, Division of Head and Neck Surgery, UCLA School of Medicine, Los Angeles 90024.

June 13-20—**Orthopedic Review.** USC at Mauna Kea, Hawaii. One week.

June 24-25—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

June 26—**Clinical Conference in Ophthalmology.** STAN. Saturday. 7 hrs. $35.

August 1-13—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. 100 hrs. $1,200 for otolaryngologists; $900, residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

August 5-6—**Keratoplasty.** PMC at Stanford Court Hotel, San Francisco. Thursday-Friday. $175.

August 6-7—**Intraocular Lens Implantation.** Santa Monica Hospital Medical Center, Santa Monica. Friday-Saturday. 16 hrs. $600. Contact: Jeanne Harris, Charlie Ruggles Ophthalmology Dept., Santa Monica Hospital Medical Center, 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

August 7-14—**Diagnosis and Management of Corneal and External Disease Problems.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

August 15-18—**Urology.** UCLA at Lake Arrowhead. Sunday-Wednesday.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

May 15—**Clinical Pharmacology Conference.** Stanford Division of Clinical Pharmacology and Palo Alto Medical Research Foundation at Stanford. Saturday. Contact: STAN.

May 17-21—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

May 19-22—**American College of Emergency Physicians, California Chapter—5th Annual Scientific Assembly.** Sheraton-Universal Hotel, North Hollywood. Wednesday-Saturday. $100 for members; $125, nonmembers. Contact: Stephanie McWilliams, Assembly Coordinator, 58 California Ave., Orinda 94563. (415) 254-1332.

May 21—**Diagnosis and Treatment of Hypertension.** See Medicine, May 21.

May 29-30—**Opportunistic Fungus Diseases.** UCSF. Saturday-Sunday.

June 4-5—**Medicine Convocation and Postgraduate Institute—21st Annual.** UCLA. Friday-Saturday.

June 7-8—**Conference on Clinical Application of Hyperbaric Oxygen—1st Annual.** Memorial Hospital Medical Center, Center for Health Education, Long Beach. Monday-Tuesday. Contact: Executive Secretary, Center for Health Education, 2801 Atlantic Ave., P.O. Box 1428, Long Beach 90801. (213) 595-3811.

June 10-12—**Management of Medical Problems for Family Physicians.** PMC at Golden Gateway Holiday Inn, San Francisco. Thursday-Saturday.

June 12—**Senility and the Aging Process.** UCLA. Saturday. $55.

June 23—**The Suicidal Patient: Recognition and Evaluation.** PMC. Wednesday. $50.

June 23-25—**Clinical Pharmacology—Rational Basis of Therapeutics.** American College of Physicians at UCSF. Wednesday-Friday. Contact: Registrar, Postgraduate Courses, ACP, 4200 Pine St., Philadelphia, PA 19104.

July 12-16—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD. Monday-Friday.

August 2-6—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday.

August 14-25—**Postgraduate Refresher Course—19th Annual.** USC, Univ. of Hawaii School of Medicine, Tripler General Hospital at Honolulu and Maui or Kauai, Hawaii. 12 days.

August 18-22—**Family Practice Refresher Course—3rd Annual.** UCLA. Wednesday-Sunday.

August 22-27—**Family Practice Refresher Course.** UCD at Del Monte Hyatt, Monterey. Sunday-Friday.

August 23-27—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD. Monday-Friday.

August 28-September 4—**Family Practice Refresher Course—7th Annual.** UCI at South Coast Plaza Hotel, Costa Mesa. One week. 46 hrs. $225. Contact: J. Blair Pace, MD, 101 City Dr. So., Orange 92668. (714) 634-5171.

August 29-September 2—**Autogenic Training.** UCLA at Asilomar. Sunday-Thursday.

August 31-October 19—**Evening Lectures in Medicine.** UCSF at Oakland Hospital, Oakland. Tuesday evenings.

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Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

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COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Providence Medical Center, 700 NE 47th Avenue, Portland 97213. Contact: Dave Gilbert, MD, Providence Medical Center:

Every Wednesday, 8:00 a.m. to 9:00 a.m.—**Spring Medical Grand Rounds.**

University of Oregon Medical School, Family Practice Center, 3181 S.W. Sam Jackson Park Road, Portland 97201:

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School.

FAMILY PRACTICE

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Family Practice Center, University of Oregon Medical School, Portland. Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

May 20—**Woodland Park Hospital Family Practice Symposium.** Woodland Park Hospital, Portland. Contact: R. T. Gustafson, MD, 10300 N.E. Hancock Street, Portland, 97220.

INTERNAL MEDICINE

May 20-22—**Oregon Society of Internal Medicine Annual Meeting.** Sunriver Lodge, Sunriver, Oregon. Contact: Donald R. Olson, MD, Oregon Society of Internal Medicine, 2164 S.W. Park Place, Portland 97205.

SURGERY

September 6-7—**Western Orthopedic Society Annual Meeting.** Sunriver Lodge, Bend. Contact: Stanley E. Donahoo, MD, 1819 West Harvard Blvd., Roseburg 97470.

OF INTEREST TO ALL PHYSICIANS

September 22-24—**Oregon Medical Association Annual Scientific Session.** Hilton Hotel, Portland. Contact: Sondra Gleason, Oregon Medical Association, 2164 S.W. Park Place, Portland 97205.

WASHINGTON, MONTANA, ALASKA and IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

May 16-20—**Pacific Coast Oto-Ophthalmological Society.** Sunday-Wednesday. Washington Plaza Hotel, Seattle. Contact: M. F. W. Smith, MD, Ear Medical Clinic of Santa Clara Valley, 2120 Forest Ave., Suite 2, San Jose, CA 95128.

May 20-21—**Pediatric Care for General Practitioners.** Thursday-Friday. Children's Orthopaedic Hospital and Medical Center, Seattle. 12 hrs. $45. Contact: William O. Robertson, MD, Dir. Med. Ed., Children's Orthopaedic Hospital and Medical Center, 4800 Sand Point Way NE, Seattle 98105. (206) 634-5072.

May 21-22—**Sports Medicine—1976.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

May 24-28—**Treating the Untreatable—Univ. of Washington School of Medicine's Montana Circuit Course.** Great Falls, 24th; Billings, 25th; Bozeman, 26th; Missoula, 27th; Whitefish/Kalispell, 28th. 4 hrs. Physicians, $25; others, $10. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 26-29—**Washington Academy of Family Physicians Annual Meeting.** Wednesday-Friday. Tyee Motor Inn, Olympia, WA. Contact: Endre Mihalyi, MD, PO Box 111, Olympia, WA 98501.

June 2-4—**Alaska State Medical Association Annual Meeting.** Wednesday-Friday. Anchorage. Contact: Alaska State Medical Association, 1135 W. 8th Ave., Anchorage, AK 99501.

June 10-11—**Hypertension: Etiology and Factors in Choice of Drugs.** Thursday-Friday. Virginia Mason Medical Center Auditorium, Seattle. 12 hrs. $75. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

June 14-17—**Disorders of Red Cell Proliferation.** (ACP). Sunday-Thursday. Rosario Resort, Orcas Island, WA. Hours to be determined. ASH, ACP members, fellows, residents, $140; non-members, $195; associates, $70. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

June 17-19—**Behavioral Methods in Medical Practice.** Thursday-Saturday. University Tower Hotel, Seattle. 8 hrs, $60. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

June 25—**Bicentennial History of Medicine in the United States.** Friday. Kane Hall, Univ. of Wash., Seattle. 6½ hrs. $75. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

July 26-29—**World of the Heart and Lung: America's Hearts and Lungs After 200 Years.** Monday-Thursday. University Tower Hotel, Seattle. 24½ hrs. $155. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

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REFERENCES

M. Ceska, R. Eriksson, and J.M. Varga
Radioimunosorbent Assay of Allergens —
The Journal of Allergy and Clinical Immunology
Vol. 49, No. 1-9, 1972

Wide L. et. al
Diagnosis of Allergy by an In Vitro Test for Allergen Antibodies
Lancet 2:1105, 1967

A. F. Lopapa, W.R. MacLaren
An In Vitro Test as used in the detection of immediate hypersensitivity in man.
V Latin American Congress of Allergy and Immunology National Academy of Medicine
Buenos Aires, Argentina, October 1974

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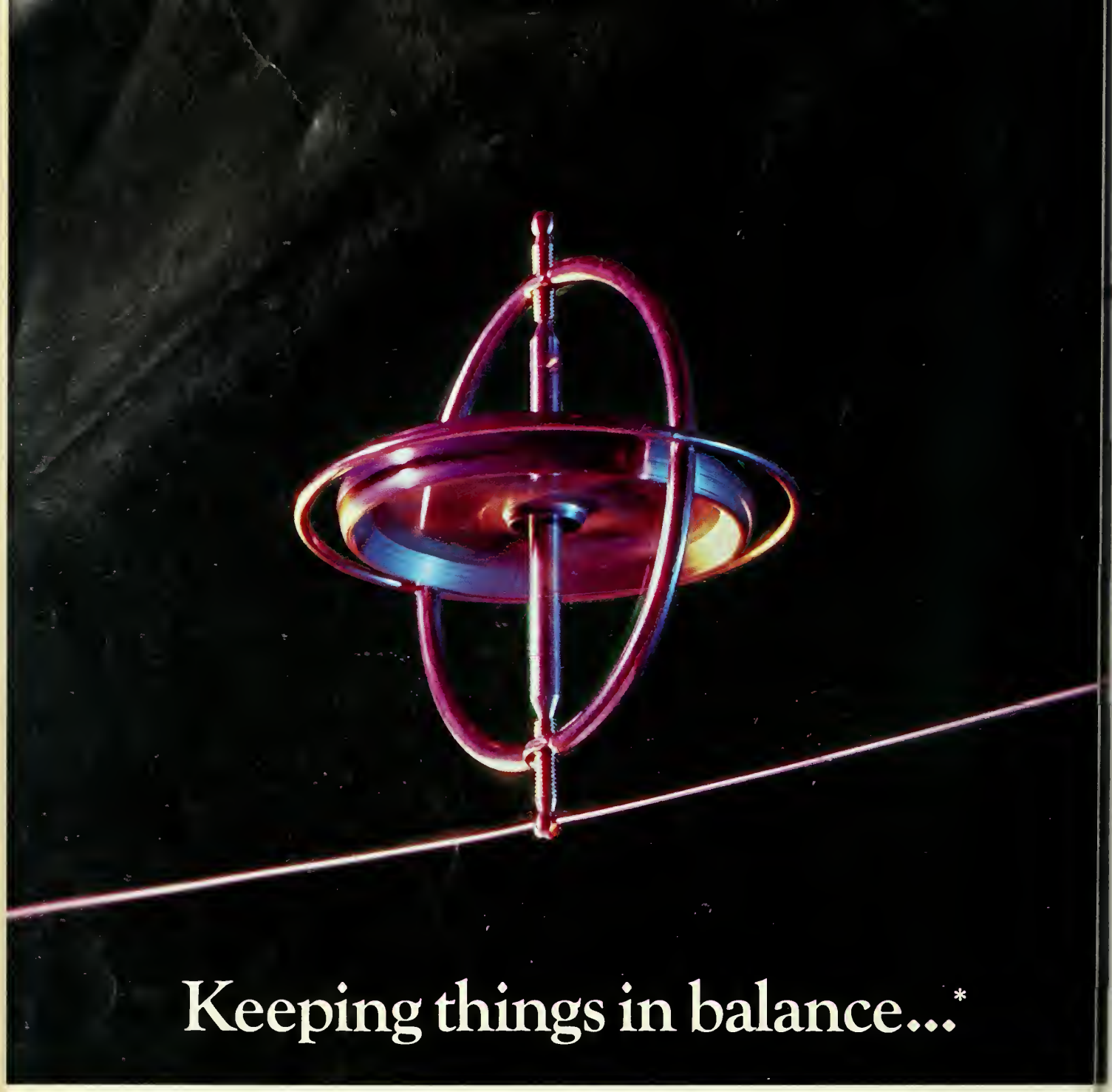

Antivert®/25 Tablets
(25 mg. meclizine HCl)

*INDICATIONS. Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:

Effective: Management of nausea and vomiting and dizziness associated with motion sickness.

Possibly Effective: Management of vertigo associated with diseases affecting the vestibular system.

Final classification of the less than effective indications requires further investigation.

CONTRAINDICATIONS. Administration of Antivert during pregnancy or to women who may become pregnant is contraindicated in view of the teratogenic effect of the drug in rats.

The administration of meclizine to pregnant rats during the 12-15 day of gestation has produced cleft palate in the offspring. Limited studies using doses of over 100 mg./kg./day in rabbits and 10 mg./kg./day in pigs and monkeys did not show cleft palate. Congeners of meclizine have caused cleft palate in species other than the rat.

Meclizine HCl is contraindicated in individuals who have shown a previous hypersensitivity to it.

WARNINGS. Since drowsiness may, on occasion, occur with use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery.

Usage in Children: Clinical studies establishing safety and effectiveness in children have not been done; therefore, usage is not recommended in the pediatric age group.

Usage in Pregnancy: See "Contraindications."

ADVERSE REACTIONS. Drowsiness, dry mouth and, on rare occasions, blurred vision have been reported.

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Effectiveness across the spectrum of most common forms of insomnia

Awake too long, awake too often, awake too early...

These are the most common forms of insomnia, and may occur singly or in any combination. The night of troubled sleep depicted here comprises all three types. As the night progresses from left to right, each sleep stage is identifiable by its own shade of gray. Blue represents "Awake."

As you can see, this hypothetical "patient" takes well over an hour to fall asleep, awakens several times during the middle of the night and awakens too early in the morning.

Sleep Stages

- Awake
- REM
- Stage 1
- Stage 2
- Stage 3
- Stage 4

Awake too long

Awake too often during the night

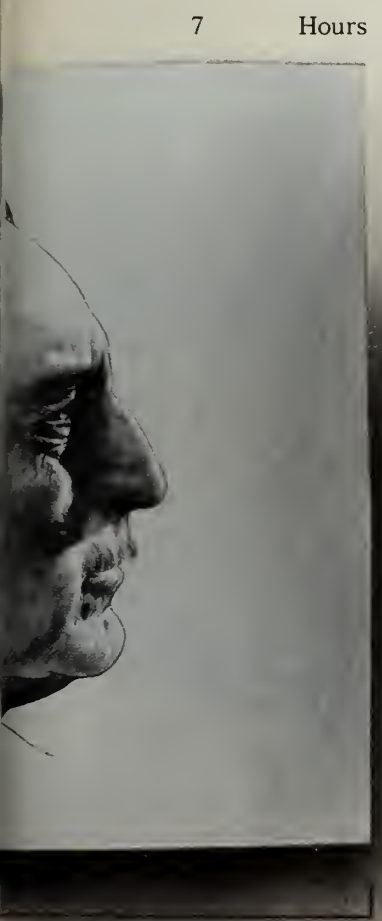
The insomnias most often occurring in young and older adults

For patients with trouble falling asleep (common in young adult insomnia patients), Dalmane (flurazepam HCl) 30 mg provides sleep within 17 minutes, on average. For those with trouble staying asleep or sleeping long enough (common in those over 50), Dalmane offers increased total sleep time with fewer nocturnal awakenings. These clinical results were demonstrated in studies conducted in four geographically separated sleep research laboratories.[1-4]

The relative safety of Dalmane (flurazepam HCl) is well documented

Dalmane (flurazepam HCl) is relatively safe and well tolerated; morning "hang-over" has been infrequent. The usual adult dosage is 30 mg; in elderly or debilitated patients, limit initial dosage to 15 mg to preclude over-sedation, dizziness or ataxia. Caution patients about possible combined effects with alcohol and other CNS depressants.

Broad-spectrum medication for the most common forms of insomnia



Awake too early

Dalmane®
(flurazepam HCl)

One 30-mg capsule *h.s.*— usual adult dosage
(15 mg may suffice in some patients).
One 15-mg capsule *h.s.*— initial dosage for elderly or debilitated patients.

- induces sleep rapidly
- reduces nighttime awakenings
- lengthens total sleep time

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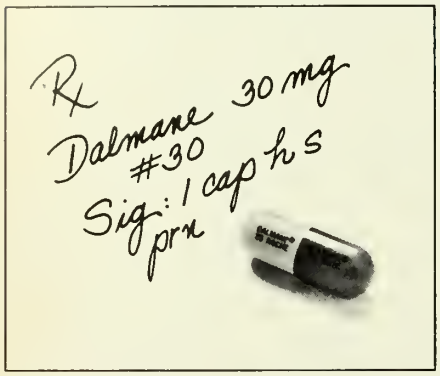
Please see following page for a summary of complete product information.

Broad-spectrum medication for the most common forms of insomnia

Dalmane®
(flurazepam HCl) Ⓒ IV



Objectively proved in the sleep research laboratory, Dalmane

- induces sleep within 17 minutes, on average
- reduces nighttime awakenings
- provides 7 to 8 hours sleep, on average, without repeating dosage

Before prescribing Dalmane (flurazepam HCl), please consult complete product information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

REFERENCES:

1. Karacan I, Williams RL, Smith JR: The sleep laboratory in the investigation of sleep and sleep disturbances. Scientific exhibit at the 124th annual meeting of the American Psychiatric Association, Washington DC, May 3-7, 1971
2. Frost JD Jr: A system for automatically analyzing sleep. Scientific exhibit at the 24th Clinical Convention of the American Medical Association, Boston, Nov 29-Dec 2, 1970; and at the 42nd annual scientific meeting of the Aerospace Medical Association, Houston, Apr 26-29, 1971
3. Vogel GW: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ
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*INDICATIONS. Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

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WARNINGS. Since drowsiness may, on occasion, occur with use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery.

Usage in Children. Clinical studies establishing safety and effectiveness in children have not been done; therefore, usage is not recommended in the pediatric age group.

Usage in Pregnancy: See "Contraindications."

ADVERSE REACTIONS. Drowsiness, dry mouth and, on rare occasions, blurred vision have been reported.

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Length of Articles—Ordinarily articles should not exceed 3,000 words (approximately 5 printed pages). Under exceptional circumstances only will articles of over 4,000 words be published.

Manuscripts—Manuscripts should be typewritten, double spaced and the *original* typescript plus one copy submitted.

Illustrations—Ordinarily publication of 2 or 3 illustrations accompanying an article will be paid for by THE WESTERN JOURNAL OF MEDICINE. Any number beyond this might have to be paid for by the author.

References—Should conform to the following order: name of author, title of article, name of periodical, with volume, inclusive pages, month and year—i.e.: Lee GS: The heart rhythm following therapy with digitalis—In theory and practice. Arch Int Med 44:554-562, Dec 1942. They should be listed in the order in which they are cited in the text, numbered in sequence and punctuated as above.

Reprints—Reprints must be paid for by the author at established standard rates.

CONTRIBUTIONS OF "LETTERS TO THE EDITOR"

The Editorial Board will be glad to receive and consider for publication letters containing information of general interest to physicians or presenting constructive criticisms on issues of the day.

"Entered as second class matter at the post office in San Francisco and additional mailing offices under the Act of March 3, 1879." Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized August 10, 1918.

Pain: a call to action.

- ☐ rapid acting
- ☐ effective, reliable oral analgesia in moderate to moderately severe pain
- ☐ oxycodone, the principal ingredient of Percodan,® is one of the more readily absorbed oral narcotic analgesics
- ☐ one tablet q.6 h.*

Percodan® Tablets

Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (Warning: May be habit forming), 0.38 mg. oxycodone terephthalate (Warning: May be habit forming), 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine. (II)

*See dosage and administration section of Brief Summary

Whenever an APC/narcotic is indicated.

DESCRIPTION Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (Warning: May be habit forming), 0.38 mg. oxycodone terephthalate (Warning: May be habit forming), 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine.

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCODAN*, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCODAN* is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCODAN* should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCODAN* may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCODAN* should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCODAN* should not be administered to children. PERCODAN*-Demi, containing half the amount of oxycodone, can be considered. (See product prescribing information for PERCODAN*-Demi.)

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCODAN* or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCODAN* should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may be occasionally necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCODAN* is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCODAN* may be additive with that of other CNS depressants. See WARNINGS.

Aspirin may enhance the effect of anticoagulants and inhibit the uricosuric effect of uricosuric agents.

MANAGEMENT OF OVERDOSAGE Signs and Symptoms Serious overdose with PERCODAN* is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur. The ingestion of very large amounts of PERCODAN* may, in addition, result in acute salicylate intoxication.

Treatment Primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonists naloxone, nalorphine or levallorphan are specific antidotes against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including oxycodone. Therefore, an appropriate dose of one of these antagonists should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

DEA Order Form Required.

PERCODAN* is a registered trademark of Endo, Inc.

Endo Inc.
Manati, Puerto Rico 00701
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)

EDO 6750

DYAZIDE®

Trademark

Each capsule contains 50 mg. of Dyrenium® (triamterene, SK&F) and 25 mg. of hydrochlorothiazide.

MAKES SENSE

TRIAMTERENE CONSERVES POTASSIUM WHILE HYDROCHLOROTHIAZIDE LOWERS BLOOD PRESSURE

FOR LONG-TERM CONTROL OF HYPERTENSION*

Serum K^+ and BUN should be checked periodically. (See Warnings Section.)

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

* **Warning**
This fixed combination drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

***Indications:** *Edema:* That associated with congestive heart failure, cirrhosis of the liver, the nephrotic syndrome; steroid-induced and idiopathic edema; edema resistant to other diuretic therapy. *Mild to moderate hypertension:* Usefulness of the triamterene component is limited to its potassium-sparing effect.

Contraindications: Pre-existing elevated serum potassium. Hypersensitivity to either component. Continued use in progressive renal or hepatic dysfunction or developing hyperkalemia.

Warnings: **Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired.** Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, **check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently**—both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 capsules; in Single Unit Packages of 100 (intended for institutional use only).

SK&F Co., Carolina, P.R. 00630
Subsidiary of SmithKline Corporation

New from
Lilly/Dista Research

NALFON®

fenoprofen calcium

A new nonsteroidal agent for relief of the signs and symptoms of rheumatoid arthritis

See following pages for prescribing information.

NALFON®
fenoprofen calcium

...reduces the pain and inflammation of rheumatoid arthritis* ...and it is well tolerated

New propionic acid derivative

NALFON® *(fenoprofen calcium)*
300-mg.† Pulvules®

- Relieves arthritic pain
- Reduces inflammation
- Improves function and mobility
- Well tolerated
- Chemically unrelated to aspirin, indomethacin, phenylbutazone, or corticosteroids

600472

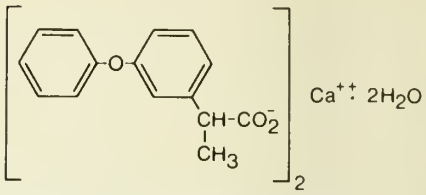
DISTA

*The safety and effectiveness of Nalfon have not been established in those rheumatoid arthritis patients who are designated by the American Rheumatism Association as Functional Class IV (largely or wholly incapacitated with patient bedridden or confined to wheelchair, permitting little or no self-care).

†Present as 345.9 mg. of the calcium salt of fenoprofen dihydrate equivalent to 300 mg. fenoprofen

Description: Pulvules® Nalfon® (fenoprofen calcium, Dista) for oral administration contain fenoprofen calcium as the dihydrate in an amount equivalent to 300 mg. of fenoprofen. Nalfon is a nonsteroidal, anti-inflammatory drug. Chemically it is a propionic acid derivative.

The structural formula is as follows:



Calcium dl-2-(3-phenoxyphenyl) propionate dihydrate.

Nalfon is a white crystalline powder, soluble in U.S.P. ethanol (95%) to the extent of approximately 15 mg./ml. at 25 C°; slightly soluble in water, and insoluble in benzene.

The pKa of Nalfon is 4.5 at 25° C.

Clinical Pharmacology: Nalfon is a nonsteroidal, anti-inflammatory, anti-arthritic compound. In animal systems, it also shows analgesic and antipyretic activity. Its mode of action is unknown. In patients with rheumatoid arthritis, the anti-inflammatory action of Nalfon has been shown by a reduction in joint swelling, a reduction in pain, a reduction in the duration of morning stiffness, a reduction in disease activity as assessed by both the investigator and the patient, and by increased mobility as demonstrated by a reduction in the number of joints with limited motion. Its action is not mediated through the adrenal gland. There is no evidence that Nalfon alters the progressive course of the underlying disease.

To further demonstrate the anti-inflammatory activity of Nalfon in humans, the emergence and degree of erythemic response were measured in adult male volunteers exposed to ultraviolet irradiation. The effects of Nalfon, aspirin, and indomethacin were compared separately with those of placebo. All three drugs demonstrated anti-erythemic activity. The results in humans confirmed the anti-inflammatory activity found in animals.

Nalfon has been shown to inhibit prostaglandin synthetase isolated from bovine seminal vesicles. Reproduction studies in rats have shown Nalfon to be associated with prolonged labor and difficult parturition when given during late pregnancy. Evidence suggested that this may be due to decreased uterine contractility resulting from the inhibition of prostaglandin synthesis.

Under fasting conditions, Nalfon is rapidly absorbed, achieving peak plasma levels of 50 mcg. per ml. within two hours of oral administration of 600 mg. doses. Good dose proportionality was observed between 200 mg. and 600 mg. in fasting male volunteers. The plasma half-life is approximately 3 hours. Approximately 90% of a single oral dose is eliminated within 24 hours as fenoprofen glucuronide and 4′-hydroxyfenoprofen glucuronide, the major urinary metabolites of fenoprofen. Fenoprofen is highly bound (99%) to albumin.

The coadministration of aspirin decreases the biologic half-life of fenoprofen due to an increase in metabolic clearance which results in a greater amount of hydroxylated fenoprofen in the urine. Although the mechanism of interaction between fenoprofen and aspirin is not totally known, enzyme induction or displacement of fenoprofen from plasma albumin binding sites are possibilities. Chronic administration of phenobarbital, a known enzyme inducer, may be associated with a decrease in plasma half-life of fenoprofen. Clinical significance of these interactions is not known.

The concomitant administration of antacid (aluminum and magnesium hydroxide) does not interfere with absorption of Nalfon. Food ingestion decreases the rate and extent of absorption of Nalfon.

With single doses of Nalfon there is less suppression of collagen-induced platelet aggregation than with aspirin.

Fenoprofen shows anti-inflammatory effects in rodents by inhibiting the development of redness

and edema in acute inflammatory conditions and by reducing soft-tissue swelling and bone damage associated with chronic inflammation. It exhibits analgesic activity in rodents by inhibiting the writhing response in mice caused by the introduction of an irritant into the peritoneal cavity and by elevating pain thresholds to pressure in edematous hindpaws of rats. In rats made febrile by the subcutaneous administration of brewer's yeast, fenoprofen produces antipyretic action. These effects are characteristic of nonsteroidal, anti-inflammatory, antipyretic, analgesic drugs.

Indications and Usage: Nalfon® (fenoprofen calcium, Dista) is indicated for relief of the signs and symptoms of rheumatoid arthritis. It is indicated in the treatment of acute flares and in the long-term management of the disease. The safety and effectiveness of Nalfon have not been established in those rheumatoid arthritis patients who are designated by the American Rheumatism Association as Functional Class IV (Incapacitated, largely or wholly bedridden, or confined to wheelchair; little or no self-care.) Improvement in patients treated with Nalfon for rheumatoid arthritis has been demonstrated by a reduction in joint swelling, a reduction in pain, a reduction in the duration of morning stiffness, a reduction in disease activity as assessed by both the investigator and the patient, and by increased mobility as demonstrated by a reduction in the number of joints with limited motion.

In clinical studies in patients with rheumatoid arthritis, Nalfon has been shown to be comparable to aspirin in controlling the aforementioned measures of disease activity but the frequency of the milder gastrointestinal adverse effects (nausea, dyspepsia) and tinnitus was less than in aspirin-treated patients. It is not known whether Nalfon causes less peptic ulceration than aspirin.

In some patients Nalfon has been used in combination with gold salts or corticosteroids. Studies have been inadequate to demonstrate whether Nalfon adds any improvement in patients maintained on gold salts or corticosteroids. Whether Nalfon could be used in conjunction with partially effective doses of corticosteroid for a "steroid-sparing" effect has not been adequately studied. The use of Nalfon in combination with salicylates is not recommended because there is no evidence to demonstrate that Nalfon would produce any additional effect beyond that produced by aspirin alone. Further, there is evidence that aspirin increases the rate of excretion of Nalfon.

There have been no studies in children; therefore the safety and effectiveness of Nalfon in children are unknown.

Contraindications: Nalfon is contraindicated in patients who have shown hypersensitivity to it.

Because the potential exists for cross sensitivity to aspirin and other nonsteroidal, anti-inflammatory drugs, Nalfon should not be given to patients in whom aspirin and other nonsteroidal, anti-inflammatory drugs induce the symptoms of asthma, rhinitis, or urticaria.

Warnings: Nalfon should be given under close supervision to patients with a history of upper gastro-intestinal tract disease and only after consulting the "ADVERSE REACTIONS" section. Gastro-intestinal bleeding, sometimes severe, has been reported in patients receiving Nalfon.

In patients with active peptic ulcer and active rheumatoid arthritis, attempts should be made to treat the arthritis with nonulcerogenic drugs, such as gold. If Nalfon must be given, the patient should be under close supervision for signs of ulcer perforation or severe gastrointestinal bleeding.

In subacute and chronic studies in rats, Nalfon caused interstitial nephritis, glomerulonephritis and renal papillary necrosis. These abnormalities were dose-related and began to appear at doses approximating the human dose. In chronic studies in monkeys interstitial nephritis also occurred following Nalfon administration. Although this was seen at doses considerably above the human dose, lower doses were not studied in this species. During the course of the clinical trials one patient developed renal failure and died with a diagnosis of septicemia, bilateral suppurative pyelonephritis and renal papillary necrosis. It is not known whether these events were drug-related. A few patients developed mild elevations of the BUN during Nalfon® (fenoprofen calcium, Dista) therapy. Since Nalfon is eliminated primarily by the kidney, the drug should not be administered to patients with significantly impaired renal function. It is desirable to perform periodic renal function tests in all patients receiving Nalfon.

Precautions: In chronic studies in rats, high doses of Nalfon caused elevation of serum transaminase and hepatocellular hypertrophy. In clinical trials, some patients developed elevation of serum transaminase, LDH, and alkaline phosphatase which persisted for some months, and usually, but not always, declined despite continuation of the drug. The significance of this is unknown. It is recommended that periodic liver function tests be performed in patients receiving Nalfon and that the drug be discontinued if abnormalities occur.

The safety of this drug in pregnancy and lactation has not been established and its use during these events is, therefore, not recommended. Reproduction studies have been performed in rats and rabbits. When fenoprofen was given to rats during pregnancy and continued to the time of labor, parturition was prolonged. Similar results have been found with other nonsteroidal, anti-inflammatory drugs which inhibit prostaglandin synthetase.

In-vitro studies have shown that fenoprofen, because of its affinity for albumin, may displace from their binding sites other drugs which are also albumin bound and may lead to drug interaction. Theoretically, fenoprofen, as well as other nonsteroidal, anti-inflammatory agents, could likewise be displaced. Patients receiving hydantoin, sulfonamides, or sulfonylureas should be observed for signs of toxicity to these drugs. In patients receiving coumarin-type anticoagulants, the addition of Nalfon to therapy could prolong the prothrombin time. Patients receiving both drugs should be under careful observation.

In patients receiving concomitant Nalfon-steroid therapy, any reduction of steroid dose should be gradual to avoid the possible complications of sudden steroid withdrawal.

Patients with initial low hemoglobin values who are receiving long term Nalfon therapy should have a hemoglobin determination at reasonable intervals.

Peripheral edema has been observed in some patients taking Nalfon; therefore, Nalfon should be used with caution in patients with compromised cardiac function.

Studies to date have not shown changes in the eye attributed to Nalfon administration. However, because of adverse eye findings in animal studies with some other nonsteroidal anti-inflammatory drugs, it is recommended that ophthalmologic studies be carried out within a reasonable period of time after starting chronic Nalfon therapy and at periodic intervals thereafter.

Since food decreases Nalfon blood levels, the drug should be given 30 minutes before or two hours after meals during the daytime.

When phenobarbital, which may enhance the metabolism of Nalfon, is added or withdrawn, Nalfon dosage adjustment may be required.

Caution should be exercised by patients whose activities require alertness if they experience central nervous system side effects from Nalfon.

Since the safety of Nalfon in patients with impaired hearing loss has not been established, these patients should have periodic tests of auditory function when chronic Nalfon therapy is given.

Nalfon decreases platelet aggregation and prolongs bleeding time. Patients who may be adversely affected by prolongation of the bleeding time should be carefully observed when Nalfon is administered.

Adverse Reactions: *Digestive System*

The most common type of adverse reaction concerned the gastro-intestinal system. Dyspepsia occurred most frequently, being observed in about one out of seven patients. Other adverse reactions in descending order of frequency were: constipation, nausea, vomiting, abdominal pain, anorexia, occult blood in the stool, diarrhea, flatulence, and dry mouth.

Three instances of peptic ulceration and/or gastro-intestinal hemorrhage that may have been due to the drug and four instances in which drug relationship was questionable were observed in 3,391 individuals to whom the drug was administered for periods of time ranging up to 165 weeks.

In less than 2% of patients the drug was discontinued because of adverse gastro-intestinal reactions.

Skin and Appendages

The most common adverse effect was pruritus which was seen in about one out of ten patients. Other adverse reactions were: rash, increased sweating, and urticaria.

In about 1% of patients Nalfon® (fenoprofen calcium, Dista) was discontinued due to an adverse effect related to the skin.

Nervous System

The most frequent adverse reaction observed was somnolence which occurred in about one out of seven patients. Other adverse effects which occurred less frequently were: dizziness, tremor, confusion, and insomnia.

Nalfon was discontinued in less than 0.2% of patients because of these side effects.

Special Senses

The most common adverse reaction was tinnitus which was seen in about one out of ten patients. Other reactions observed in descending order of frequency were: blurred vision and decreased hearing.

In about 0.2% of patients Nalfon was discontinued due to adverse effects related to the special senses.

Cardiovascular

The most frequent adverse event observed was palpitations. This was noted in about one out of 25 patients. Tachycardia was observed less frequently.

In less than 0.5% of patients Nalfon was discontinued due to cardiovascular adverse reactions.

Laboratory

Anemia was noted in about one out of 500 patients. One patient required discontinuation of Nalfon therapy due to anemia. Increase in alkaline phosphatase, LDH, and SGOT were observed. ("See Precautions.")

Miscellaneous

Headache was seen in about one out of seven patients. Less frequently observed in descending order of frequency were: nervousness, asthenia, dyspnea, peripheral edema, fatigue, malaise, dysuria.

Overdosage: No specific information is available on the treatment of overdosage with Nalfon. If it should occur, standard procedures to evacuate gastric contents and to support vital functions should be employed. Since Nalfon is acidic and is excreted in the urine, it may be beneficial to administer alkali and induce diuresis. Furosemide (Lasix®) did not lower blood levels.

Dosage and Administration: For the initial treatment of rheumatoid arthritis, the recommended oral dose is 600 mg. four times a day. Although improvement may be seen in a few days in many patients, an additional two to three weeks may be required to gauge the full benefits of therapy. The dosage should be adjusted in accordance with the patient's condition and changes in disease activity. Daily dosage larger than 3200 mg. is not recommended. Nalfon should be administered 30 minutes before or at least two hours after meals. If gastro-intestinal complaints occur, administer Nalfon with meals or milk.

There have been no studies in children; therefore, the safety and effectiveness of Nalfon in children are unknown.

How Supplied: Pulvules Nalfon, 300 mg. (equivalent to fenoprofen), are supplied in bottles of 60 and 500 (No. 416). They are yellow and ocher in color. The Identi-Code® (formula identification code, Dista) symbol is H77.

DISTA 600472

Additional information available to the profession on request.

DISTA PRODUCTS COMPANY
Division of Eli Lilly and Company
Indianapolis, Indiana 46206

How many of your patients know the Four Food Groups?

They probably think they know what protein, minerals and vitamins are. But can they apply that knowledge to the food they eat?

USDA's Four Food Groups categorizes foods according to their nutrients. Such a system makes it easier for your patients to follow a balanced diet.

For attractive color copies of the Four Food Groups guide for patients, write: Dairy Council of California, Box 28F, Sacramento, CA 95825.

Dairy Council of California

The Four Food Groups—milk, meat, vegetables and fruits, breads and cereals—a practical guide to good nutrition.

BIOFEEDBACK TRENDSETTERS FROM ASI

Shown is ASI's array of feedback myographs. Other series include feedback encephalographs, thermometers, dermographs, matrixes, and data acquisition centers.

If you believe your patient's condition involves significant psychological or psychosomatic components, you may find biofeedback therapy to be an effective aid to the overall treatment picture.

Autogenic Systems

Autogenic Systems, America's largest manufacturer of biofeedback instrumentation, offers a complete line of biofeedback instruments of exceptional high quality and reliability at surprisingly reasonable prices. ASI's lowest priced instruments frequently offer specifications superior to the top line instruments of competing companies. Autogenic Systems is able to offer these instrumentation values because of:

Superior Engineering

ASI has by far the largest engineering staff in the industry. This team of analog, digital, biomedical, computer and electromechanical professionals has produced the most comprehensive biofeedback product line available today. This product line demonstrates ASI's engineering proficiency through its innovative design approaches that both lower costs and improve specifications. These design advances have resulted in a variety of important patents defining the present biofeedback instrumentation state of the art. And because of Autogenic Systems' large volume sales, engineering development cost for each instrument is spread over a large number of units.

Large Volume Production

Being the largest manufacturer of biofeedback instrumentation, ASI can pass along the savings of mass production to its customers. Mass scheduled purchases of semiconductors and other raw materials, coupled with sophisticated assembly line procedures, have resulted in substantial savings.

Computer Controlled Efficiency

Autogenic Systems' IBM computer allows maximized efficiency in inventory control, production scheduling, costing, and the allocation of resources. Advanced computer programs are applied to most areas of the company and result in optimized operational efficiency. Furthermore, specialized scientific and manufacturing computers are being used in engineering for research and design and in production for automated printed circuit card testing.

Quality Control

ASI has the industry's most elaborate quality control procedures including industrial oven module burn-in and 18 hour monitored power-on testing. All instruments must meet scores of performance parameters before shipment to customers.

More For Your Money Includes:

A very substantial software program prepared by ASI in conjunction with many prominent biofeedback clinicians (medical and psychological). This three-volume series includes physiology and biomedical instrumentation overviews, extensive applications information, a large collection of protocols prepared by leading clinicians, a substantial body of case studies, the largest biofeedback bibliography available, and administrative and set-up procedures.

Systems oriented instrumentation that will interface into ASI's wide range of biofeedback accesories and peripherals, including our line of computing multi-channel data acquisition centers, matrixed color CRT, visual and weighted matrixed audio systems, differential/ratiometric systems for muscle symmetry training, industry state of the art optical isolators, power supplies and multiple station switching centers.

Service provided by experienced electrical engineers, technicians and biomedical engineers facilitating the use of biofeedback instrumentation from the single practice office to major medical installations.

Product Demonstrations

Product demonstrations are available for professionals anywhere in North America. Any Autogen unit can be sent to you on a 10-day trial period. For further information, return the coupon below. We welcome your inquiries and comments.

Please send complete literature **D-12**

Name _____

Position _____

Institution _____

Street _____

City _____ **State** _____ **Zip** _____

Field of Interest _____

ASI

Autogenic Systems, Inc.
809 Allston Way
Berkeley, California 94710
(415) 548-6056

In two separate multicenter studies* of patients with chronic or frequently recurrent urinary tract infections

10 days of Bactrim™ therapy produced better results in maintaining clear cultures than:

- 10 days of ampicillin therapy
- 28 days of cephalexin therapy

*Protocols identical except for drug administered and duration of therapy. Protocol details on last page of this advertisement.

Please see summary of product information on last page of this advertisement.

ROCHE

Roche
Research
U.T.I. Study
No. 2

)ne month after therapy ceased, a higher percentage f Bactrim-treated patients maintained clear cultures*.

	No. of patients	Therapy	% of clear cultures*
Study No. 1	80	10-day Bactrim	71.3%
	76	10-day ampicillin	56.6%
Study No. 2	60	28-day cephalexin	56.7%

*rion for clear culture: 1000 or fewer organisms/ml of urine.

month after therapy: 10 days of Bactrim maintained r cultures for one month in a larger percentage of ents than either of the other agents. The maintenance ear cultures for one month after therapy has ended particular importance for patients whose problems chronic or recur frequently, for it is during this period relapse or reinfection often occurs.

ediately after therapy: Here again, Bactrim results superior. At the end of therapy, 90.4% of 83 patients) days of Bactrim had clear cultures, compared with 81.7% of 82 patients on 10 days of ampicillin and 86.6% of 82 patients on 28 days of cephalexin.

Adverse reactions: Side effects in these studies were relatively mild (*e.g.*, nausea, vomiting, rash), but more serious adverse effects can occur with the agents studied. For a complete list of adverse reactions with each drug, please consult the manufacturer's product information.

Note: Bactrim single strength tablets were used in these clinical trials. However, studies have established the bioequivalency of one Bactrim DS tablet with two single strength Bactrim tablets.

Bactrim™
) trimethoprim and 400 mg sulfamethoxazole)
blets

Bactrim™ **DS**
(160 mg trimethoprim and 800 mg sulfamethoxazole)
Double Strength tablets

For chronic or frequently recurrent cystitis
pyelonephritis due to susceptible organisms.

For longer lasting results in chronic or frequently recurrent cystitis or pyelonephritis

Bactrim™

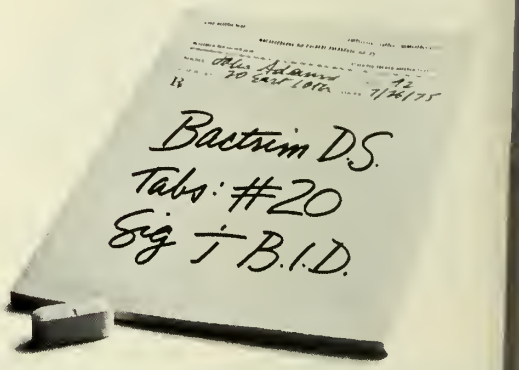
(80 mg trimethoprim and 400 mg sulfamethoxazole)

tablets

Bactrim™ DS

(160 mg trimethoprim and 800 mg sulfamethoxazole)

Double Strength tablets



Protocols

While results came from separate studies, protocols were identical with few exceptions:

Equivalencies: Patients selected were asymptomatic with chronic significant bacteriuria or had suffered a recurrence of previously treated symptomatic disease; significant bacteriuria was established as 100,000 or more of same organisms/ml urine in 2 consecutive cultures within 7 days; patient exclusions for reasons of safety or efficacy were identical; the same baseline laboratory studies were made at the same intervals; identical criteria were used to measure success or failure; clear culture was considered as 1000 or fewer organisms/ml urine.

Exceptions: Drug regimens differed (Study #1, two Bactrim tablets b.i.d. or one 500-mg ampicillin capsule q.i.d. for 10 days; Study #2, one 250-mg cephalexin pulvule q.i.d. for 28 days); pretreatment organisms had to be susceptible to ampicillin or cephalexin, but not necessarily to Bactrim.

For more detailed information on the two separate multicenter studies (see previous pages) in which Bactrim achieved better results than ampicillin or cephalexin in maintaining clear cultures, write to:

Professional Services Department
Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Chronic urinary tract infections evidenced by persistent bacteriuria (symptomatic or asymptomatic), frequently recurrent infections (relapse or reinfection), or infections associated with urinary tract complications, such as obstruction. Primarily for cystitis, pyelonephritis or pyelitis due to susceptible strains of *E. coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris* and *Proteus morganii.*

NOTE: The increasing frequency of resistant organisms limits the usefulness of antibacterials, especially in these urinary tract infections. The recommended quantitative disc susceptibility method (*Federal Register, 37*:20527-20529, 1972) may be used to estimate bacterial susceptibility to Bactrim. A laboratory report of "Susceptible to trimethoprim-sulfamethoxazole" indicates an infection likely to respond to Bactrim therapy. If infection is confined to the urine, "Intermediate susceptibility" also indicates a likely response. "Resistant" indicates that response is unlikely.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy; nursing mothers.

Warnings: Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted. **Data are insufficient to recommend use in infants and children under 12.**

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L. E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for children under 12. Usual adult dosage: 1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days.

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) every 24 hours
Below 15	Use not recommended

Supplied: Double Strength (DS) tablets, each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100; Tel-E-Dose® packages of 100. Tablets, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole — bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40, available singly and in trays of 10.

Oral suspension, containing in each teaspoonful (5 ml) the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole; fruit-licorice flavored — bottles of 16 oz (1 pint).

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Upjohn

The Upjohn Company, Kalamazoo, Michigan 49001

Medrol® 4 mg Dosepak*

methylprednisolone, Upjohn

The explicit printed dosage instructions that accompany each Dosepak make it easy for the patient to understand and follow the dosage regimen.

*Trademark

48-7-4

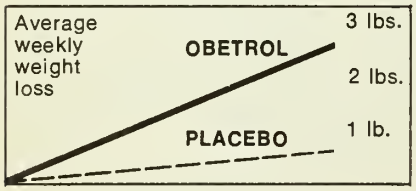
EFFECTIVE APPETITE DEPRESSANT with predictable pharmacological action

OBETROL® CII

Single entity amphetamine product. Each OBETROL-10 (10 mg. tablet) contains: dextroamphetamine saccharate 2.5 mg., amphetamine aspartate 2.5 mg., dextroamphetamine sulfate 2.5 mg., amphetamine sulfate 2.5 mg. OBETROL-20 (20 mg. tablets) contain twice this potency.

Average weight loss of 2.15 lbs per week compared in clinical studies against a placebo.

CONTROLLED STUDY —
72 CASES 4 WEEKS' RESULTS



Obetrol eases the discomfort of adherence to a restricted diet in individuals who are well motivated to reduce their food intake.

Clinical studies disclose amphetamines to be the most dependable drug in a weight-reduction regimen compared to other anorexigenic agents.

Amphetamines have a significant potential for abuse. In view of their limited short-term anorectic effect and rapid development of tolerance, they should be used with extreme caution and only for limited periods of time in weight reduction programs.

Actions: Amphetamines are sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. The anorectic effect diminishes after a few weeks.

Indications: Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. For patients in whom obesity is refractory to other measures.

Contraindications: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncracy to the sympathomimetic amines. • Agitated states. • Patients with a history of drug abuse. • During or within 14 days following the administration of monoamine oxidase inhibitors, hypertensive crises may result.

Warnings: Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

Precautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen. Amphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Adverse Reactions: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic:* Urticaria. *Endocrine:* Impotence, changes in libido.

Dosage and Administration: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening medication should be avoided because of the resulting insomnia.

1. Narcolepsy: Usual dose 5 to 60 milligrams per day in divided doses.
2. Minimal brain dysfunction:
   a. Not recommended for children under 3 years of age.
   b. Children from 3 to 5 years of age: 2.5 milligrams daily, raised in increments of 2.5 milligrams at weekly intervals until optimal response is obtained.
   c. Children 6 years of age and older, 5 milligrams, once or twice daily, increased in increments of 5 milligrams at weekly intervals. Only in rare cases will it be necessary to exceed a total of 40 milligrams per day.
3. Obesity: Usual adult dose 5 to 30 milligrams per day in divided doses.

Overdosage: Manifestations of acute overdosage with amphetamines include restlessness, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.

Management of acute amphetamine intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations in this regard.

Availability: Supplied in bottles of 100; 500 and 1,000 tablets.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

January 1973

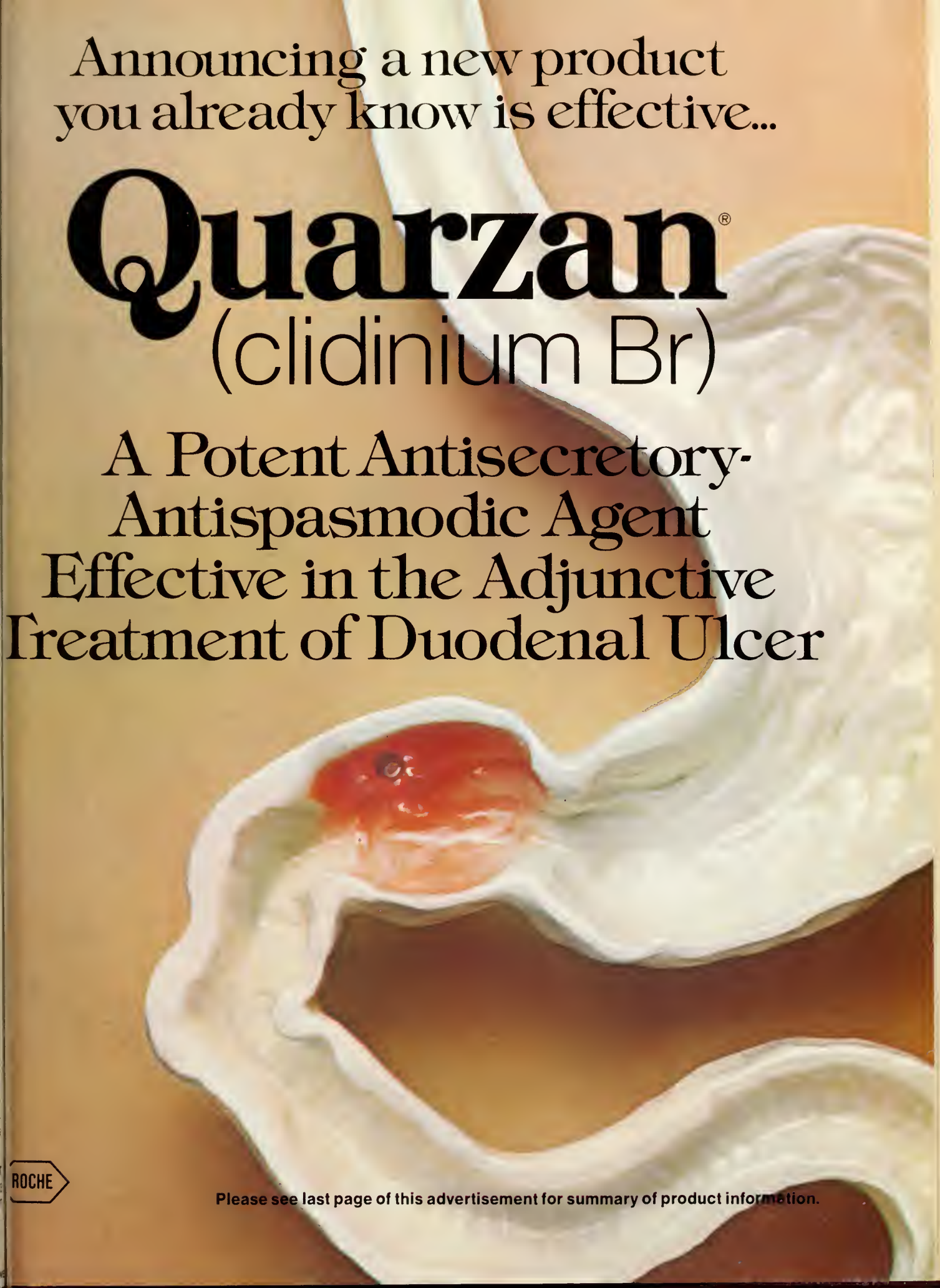
Comprehensive informational brochure available upon written request. Prescribe Obetrol for appetite control.

OBETROL Pharmaceuticals Division/Rexar Pharmacal Corp. Valley Stream, New York 11582

Announcing a new product you already know is effective...

Quarzan®
(clidinium Br)

A Potent Antisecretory-Antispasmodic Agent Effective in the Adjunctive Treatment of Duodenal Ulcer



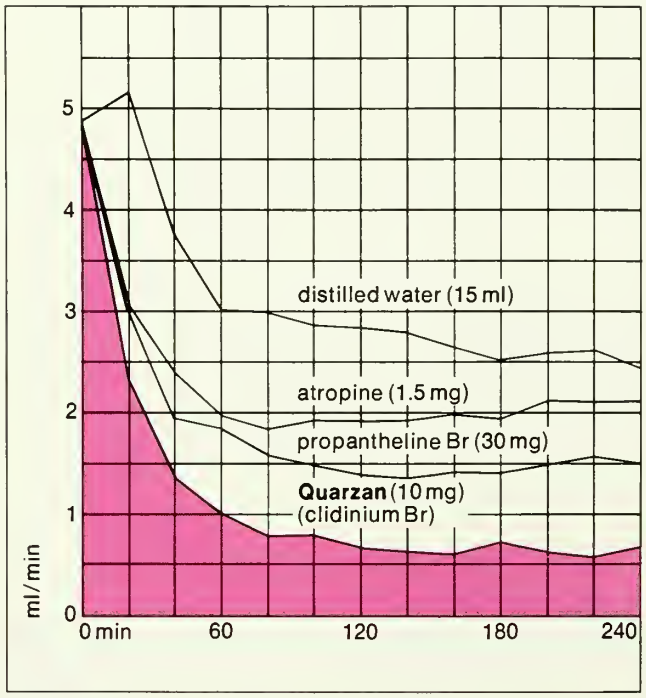
ROCHE

Please see last page of this advertisement for summary of product information.

Quarzan®
(clidinium Br)

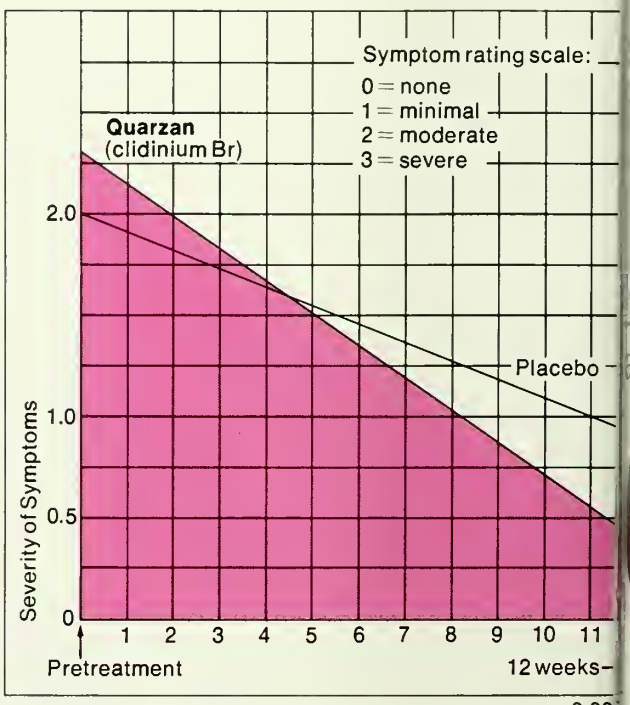
Provides the anticholinergic action of Librax—controls the pain and spasm due to excessive gastric secretion and G.I. motility

Volume of Gastric Flow Reduced



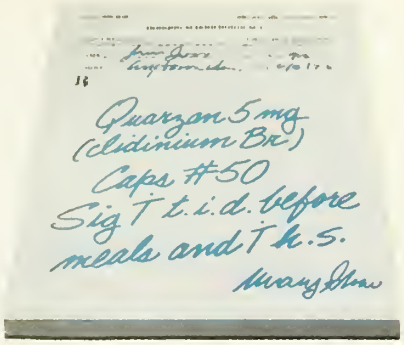
Study in normal human subjects shows marked decrease in gastric secretion with Quarzan, comparing favorably with reference drugs.*

Upper Abdominal Pain Relieved in 12-Week Study



Mean changes in symptom scores in duodenal ulcer patients show the effectiveness of Quarzan (clidinium Br).*

*Data on file, Medical Dept., Hoffmann-La Roche Inc.



An important part of the treatment plan for management of duodenal ulcer

Quarzan (clidinium Br)

1 Provides effective control of both pain and G.I. distress.

2 Provides potent antisecretory-antispasmodic action.

3 Offers a wide margin of safety—no known specific drug interactions.

4 Permits flexibility of dosage to meet individual needs.

Special considerations

Quarzan is contraindicated in patients with glaucoma, obstructive uropathy or known hypersensitivity to clidinium Br or other anticholinergic drugs. (See product information for complete list of contraindications.) For the aged and debilitated, one 2.5-mg capsule t.i.d. before meals is recommended.

A new therapeutic choice for effective antisecretory-antispasmodic action

Quarzan®

(clidinium Br)

2.5 mg and 5 mg capsules

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Please see following page for summary of product information.

The antisecretory-antispasmodic action of Librax® now available as a single entity

Each capsule contains 5 mg chlordiazepoxide HCl
and 2.5 mg clidinium Br

Quarzan®
(clidinium Br)

2.5 mg and 5 mg capsules

Quarzan®
(clidinium Br)

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Quarzan (clidinium Br) is effective as adjunctive therapy in peptic ulcer disease. **Anticholinergics have not been shown to be effective in contributing to the healing of peptic ulcer, decreasing the rate of recurrence or preventing complications.**
Contraindications: Known hypersensitivity to clidinium bromide or to other anticholinergic drugs, glaucoma, obstructive uropathy, obstructive disease of the gastrointestinal tract, paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis.
Warnings: Anticholinergics may produce drowsiness or blurred vision; caution about activities requiring mental alertness. Heat prostration due to decreased sweating in high temperatures may occur. Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. Use of anticholinergics in patients with suspected intestinal obstruction would be inappropriate and possibly harmful. With overdosage, a curare-like action may occur.
Usage in Pregnancy and Nursing Mothers: Use of any drug in pregnancy or in women of childbearing potential requires that the poter tial benefit of the drug be weighed against the possible hazards t mother and fetus. As a general rule, anticholinergics should not b used by nursing mothers; their safety and efficacy in children ha not been established.
Precautions: Exercise caution in elderly and in patients with aut nomic neuropathy, hepatic or renal disease, ulcerative colitis, hype thyroidism, cardiac conditions, hypertension, prostatic hypertroph and hiatal hernia associated with reflux esophagitis.
Adverse Reactions: As with other anticholinergics, most frequentl reported adverse effects are dryness of mouth, blurring of visior urinary hesitancy and constipation. Other effects reported: decrease sweating, urinary retention, tachycardia, palpitations, dilation of th pupils, cycloplegia, increased ocular tension, loss of taste, headache nervousness, mental confusion, drowsiness, weakness, dizziness, ir somnia, nausea, vomiting, bloated feeling, impotence, suppression c lactation and severe allergic reactions including anaphylaxis, urt caria and other dermal manifestations.
Usual Daily Dosage: Individualize for maximum beneficial effects Adults: 2.5 to 5 mg *t.i.d.* or *q.i.d.* a.c. and *h.s.* Geriatric or debilitate patients: 2.5 mg *t.i.d.* a.c. Desired pharmacological effect unlikel to be attained without occasional side effects.
Supplied: Quarzan (clidinium Br) capsules, 2.5 mg (green and re and 5 mg (green and grey)—bottles of 100 and 500; Prescriptio Paks of 50, available singly and in trays of 10.

Librax®
Each capsule contains 5 mg chlordiazepoxide HCl
and 2.5 mg clidinium Br.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Patients with glaucoma; prostatic hypertrophy and benign bladder neck obstruction; known hypersensitivity to chlordiazepoxide hydrochloride and/or clidinium bromide.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering Librium® (chlordiazepoxide hydrochloride) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards. As with all anticholinergic drugs, an inhibiting effect on lactation may occur.
Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude development of ataxia, oversedation or confusion (not more than two capsules per day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacologic effects of agents, particularly potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic functior Paradoxical reactions (e.g., excitement, stimulation and acute rage have been reported in psychiatric patients. Employ usual precaution in treatment of anxiety states with evidence of impending depre sion; suicidal tendencies may be present and protective measure necessary. Variable effects on blood coagulation have been reporte very rarely in patients receiving the drug and oral anticoagulant causal relationship has not been established clinically.
Adverse Reactions: No side effects or manifestations not seen wit either compound alone have been reported with Librax. When chlo diazepoxide hydrochloride is used alone, drowsiness, ataxia and co fusion may occur, especially in the elderly and debilitated. Thes are avoidable in most instances by proper dosage adjustment, b are also occasionally observed at the lower dosage ranges. In a fe instances syncope has been reported. Also encountered are isolate instances of skin eruptions, edema, minor menstrual irregularitie nausea and constipation, extrapyramidal symptoms, increased an decreased libido—all infrequent and generally controlled with dosag reduction; changes in EEG patterns (low-voltage fast activity) ma appear during and after treatment; blood dyscrasias (including agra ulocytosis), jaundice and hepatic dysfunction have been reported o casionally with chlordiazepoxide hydrochloride, making period blood counts and liver function tests advisable during protracted the apy. Adverse effects reported with Librax are typical of anticholine gic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hes tancy and constipation. Constipation has occurred most often whe Librax therapy is combined with other spasmolytics and/or lo residue diets.
Dosage: Individualize for maximum beneficial effects. Usual mai tenance dose is 1 or 2 capsules, 3 or 4 times a day, before meals an at bedtime. Geriatric patients—see Precautions.
How Supplied: Librax® Capsules, each containing 5 mg chlordia epoxide hydrochloride (Librium®) and 2.5 mg clidinium bromic (Quarzan®)—bottles of 100 and 500; Prescription Paks of 50, avai able singly and in trays of 10.

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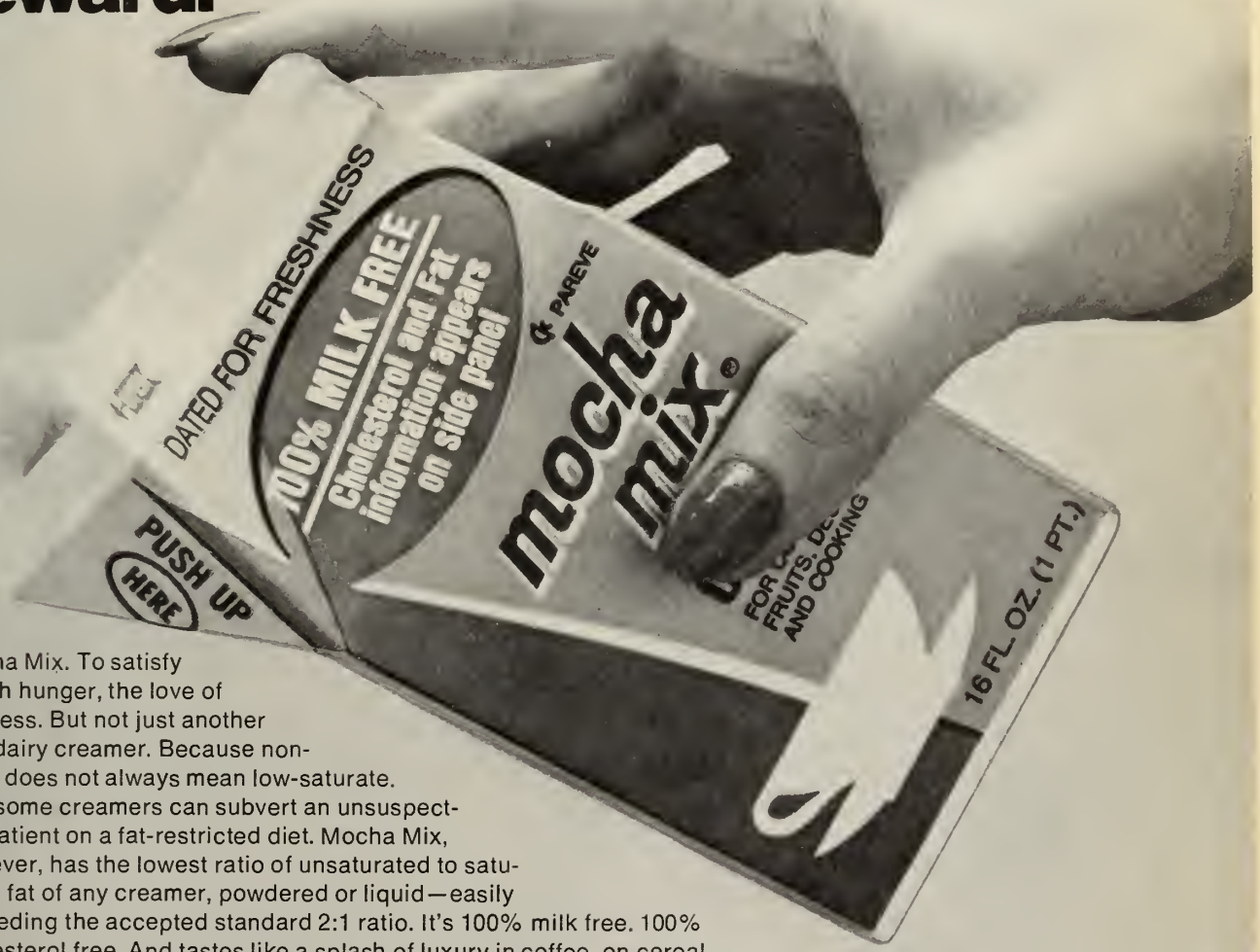
Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley New Jersey 07110

What to do when your patient feels robbed of milk, cream and saturated fat.

Offer a reward.



Mocha Mix. To satisfy mouth hunger, the love of richness. But not just another non-dairy creamer. Because non-dairy does not always mean low-saturate. And some creamers can subvert an unsuspecting patient on a fat-restricted diet. Mocha Mix, however, has the lowest ratio of unsaturated to saturated fat of any creamer, powdered or liquid—easily exceeding the accepted standard 2:1 ratio. It's 100% milk free. 100% cholesterol free. And tastes like a splash of luxury in coffee, on cereal, fruit, dessert, even in cooking. If you must deprive your patient, add a reward for good behavior. Mocha Mix.

MOCHA MIX DATA SHEET

Portion Size 1 Fluid Ounce (2 Tbs.)

Servings per container	16
Calories	40
Protein	0 grams
Carbohydrate	3 grams
Fat	3 grams
Percent of Calories from Fat	73%
Polyunsaturated Fat	1 gram
Saturated Fat	0 grams
Cholesterol	0

(Percentage of U.S. Recommended Daily Allowances (U.S., RDA)*

*Contains less than 2% of the U.S. RDA of Protein, Vitamin A, Vitamin C, Thiamine, Riboflavin, Niacin, Calcium, Iron.

In addition to the pint and quart size found in the dairy case of most grocery stores, Mocha Mix is available in 4 ounce and ½ oz. portion packs for hospitals and institutions.

Interested? Send us a note and we will send you a supply of coupons your patients can redeem at their grocers. Hospital service may also be supplied upon request. Mail to:

Mocha Mix Dept. Presto Food Products, Inc.
P.O. Box No. 21908, Los Angeles, Calif. 90021

mocha mix® ...the non-dairy creamer that's lowest in saturated fat.

Testing in Humans: Who, Where & When.

the weight of ethical opinion:

Few would disagree that the effectiveness and safety of any therapeutic agent or device must be determined through clinical research.

But now the *practice* of clinical research is under appraisal by Congress, the press and the general public. Who shall administer it? On whom are the products to be tested? Under what circumstances? And how shall results be evaluated and utilized?

The Pharmaceutical Manufacturers Association represents firms that are significantly engaged in the discovery and development of new medicines, medical devices and diagnostic products. Clinical research is essential to their efforts. Consequently, PMA formulated positions which it submitted on July 11, 1975, to the Subcommittee on Health of the Senate Labor and Public Welfare Committee, as its official policy recommendations. Here are the essentials of PMA's current thinking in this vital area.

1. PMA supports the mandate and mission of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and offers to establish a special committee composed of experts of appropriate disciplines familiar with the industry's research methodology to volunteer its service to the Commission.

2. PMA supports the formation of an independent, expert, broadly based and representative panel to assess the current state of drug innovation and the impact upon it of existing laws, regulations and procedures.

3. When FDA proposes regulations, it should prepare and publish in the *Federal Register* a detailed statement assessing the impact of those regulations on drug and device innovation.

4. PMA proposes that an appropriately qualified medical organization be encouraged to undertake a comprehensive study of the optimum roles and responsibilities of the sponsor and physician when company-sponsored clinical research is performed by independent clinical investigators.

5. PMA recognizes that the physician-investigator has, and should have, the ultimate responsibility for deciding the substance and form of the informed consent to be obtained. However, PMA recommends that the sponsor of the experiment aid the investigator in discharging this important responsibility by providing (1) a document detailing the investigator's responsibilities under FDA regulations with regard to patient consent, and (2) a written description of the relevant facts about the investigational item to be studied, in comprehensible lay language.

6. In the case of children, the sponsor must require that informed consent be obtained from a legally appropriate representative of the participant. Voluntary consent of an older child, who may be capable of understanding, in addition to that of a parent, guardian or other legally responsible person, is advisable. Safety of the drug or device shall have been assessed in adult populations prior to use in children.

7. PMA endorses the general principle that, in the case of the mentally infirm, consent should be sought from both an understanding subject and from a parent or guardian, or in their absence, another legally responsible person.

8. Pharmaceutical manufacturers sponsoring investigations in prisons must take all reasonable care to assure that the facilities and personnel used in the conduct of the investigations are suitable for the protection of participants, and for the avoidance of coercion, with a respect for basic humanitarian principles.

9. Sponsors intending to conduct non-therapeutic clinical trials through the participation of employee volunteers should expand the membership and scope of its existing Medical Research Committee, or establish such an internal Medical Research Committee, with responsibility to approve the consent forms of all volunteers, designs, protocols and the scope of the trial. The Committee should also bear responsibility to ensure full compliance with all procedures intended to protect employee volunteers' rights.

10. Where the sponsor obtains medical information or data on individuals, it shall be accorded the same confidential status as provided in codes of ethics governing health care professionals.

11. PMA and its member firms accept responsibility to aid and encourage appropriate follow-up of human subjects who have received investigational products that cause latent toxicity in animals or, during their use in clinical investigation, are found to cause unexpected and serious adverse effects.

12. PMA supports the exploration and development by its member companies of more systematic surveillance procedures for newly marketed products.

13. When a pharmaceutical manufacturer concludes, on the basis of early clinical trials of a basic new agent, that a new drug application is likely to be submitted, a proposed development plan accompanied by a summary of existing data, would be submitted to the FDA. Following a review of this submission, the FDA, and its Advisory Committee where appropriate, would meet with the sponsor to discuss the development plan. No *formal* FDA approval should be required at this stage. Rather, the emphasis should be on identification of potential problems and questions for the sponsor's further study and resolution as the program develops.

The PMA believes that health professionals as well as the public at large should be made aware of these 13 points in its Policy on Clinical Research. For these recommendations envisage constructive, cooperative action by industry, research institutions, the health professions and government to encourage creative and workable responses to issues involved in the clinical investigation of new products.

P·M·A

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W.
Washington, D. C. 20005

Classified Advertisements

The rate for each insertion is **$2.50 per line** (average six words per line) **with five line minimum.**

Box number charge: $1.50 each month.

Classified display rates $25.00 per inch.

Copy for classified advertisements should be received not later than **the fifth of the month preceding issue.** • Classified advertisers using Box Numbers forbid the disclosure of their identity. Your inquiries in writing will be forwarded to Box Number advertisers. The right is reserved to reject or modify all classified advertising copy in conformity with the rules of the Advertising Committee.

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PHYSICIANS WANTED

INTERNISTS—Board Certified/Eligible, to joln. 20-man department in 45-man Multi-specialty group. Beautiful coastal area. W. Richard Ellis, Administrator, P.O. Drawer LL, Santa Barbara, CA 93102.

IMMEDIATE OPENING for full-time physician to join Medical Division of large international petrochemical company in Midwest. Board certified In internal medicine, or would consider board qualified. Salary negotiable, plus numerous company benefits. Anyone interested should respond to Phillips Petroleum Company, Medical Director, B 57 Adams Building, Bartlesville, OK 74004.

OB/GYN AND INTERNAL MEDICINE—Semi-rural community, 15 miles southeast of Madison, WI. Area population 25,000 excellent working and living environment incentives/guarantee. Contact: Stoughton Community Hospital Foundation Director, 900 Ridge St., Stoughton, WI 53589; (608) 873-6611.

New and Exclusive

SPHERULIN

A Better Diagnostic Skin Test for Coccidioidomycosis

- **35% more positive reactors**
- **Fewer second tests required**
- **Greater sensitivity: no loss of specificity**
- **Prepared from the spherule phase of *Coccidioides immitis***

Usual Skin Test Strength — 1.0 ml. vial
High Skin Test Strength — 0.5 ml. vial

For literature and price information, contact

BERKELEY BIOLOGICALS

Second and Hearst Streets • Berkeley, CA 94710
Phone (415) 843-6846

PHYSICIANS WANTED

ALLERGIST, IMMUNOLOGIST—Certified/Eligible to join as second man in department of 45-man Multi-specialty group. Beautiful coastal area. W. Richard Ellis, Administrator, P.O. Drawer LL, Santa Barbara, CA 93102.

INTERNIST, CARDIOLOGIST, ORTHOPEDIC SURGEON AND FAMILY PRACTICE PHYSICIANS WANTED. Malpractice rates $500 per year for $1 million coverage. Beautiful country, medical school affiliation, guarantee, call collect (309) 647-3193. Contact: Dr. Schmidt or Mansfield, Graham Hospital, Canton, IL 61520.

WANTED: Pediatrician and Family Practitioners by an eight-man group in Northeastern Wisconsin. Marinette has a population of 13,000 and its sister-city Menominee, Michigan has 12,000. Located on the beautiful waters of Green Bay, there are abundant recreational opportunities, excellent schools and modern hospital facilities. $40,000 salary first year, full corporate status second year. All fringes, including malpractice insurance, paid by clinic. Contact: Gerard De Bruin, Business Manager, Boren Clinic, 1510 Main St., Marinette, Wis. 54143.

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(Continued on Page 40)

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IN GONORRHEA

INJECTION

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(STERILE PENICILLIN G PROCAINE SUSPENSION) WYETH

In **Gonorrhea,** the drug regimen of choice is aqueous penicillin G procaine. In uncomplicated cases, administration of 4.8 million units together with 1 gram oral probenecid, given just before injection, is recommended.

Indications: In treatment of moderately severe infections due to penicillin G-sensitive microorganisms sensitive to the low and persistent serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: When high sustained serum levels are required use aqueous penicillin G, IM or IV.

The following infection will usually respond to adequate dosages of intramuscular penicillin G procaine—*N. gonorrhoeae:* acute and chronic (without bacteremia).

For deep intramuscular injection only.

Contraindication: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well-documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents, e.g., pressor amines, antihistamines, and corticosteroids.

Immediate toxic reactions to procaine may occur in some individuals, particularly when a large single dose is administered in the treatment of gonorrhea (4.8 million units). These reactions may be manifested by mental disturbances, including anxiety, confusion, agitation, depression, weakness, seizures, hallucinations, combativeness, and expressed "fear of impending death". The reactions noted in carefully controlled studies occurred in approximately one in 500 patients treated for gonorrhea. Reactions are transient, lasting from 15-30 minutes.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 ml. of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparations should not be used. Antihistaminics appear beneficial in treatment of procaine reactions.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy, discontinue penicillin and take appropriate measures.

If allergic reaction occurs, withdraw penicillin unless in the opinion of the physician, the condition being treated is life threatening and amenable only to penicillin therapy.

When treating gonococcal infections with suspected primary or secondary syphilis, perform proper diagnostic procedures, including darkfield examinations. In all cases in which concomitant syphilis is suspected, perform monthly serological tests for at least four months.

Adverse Reactions: (Penicillin has significant index of sensitization) skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; serum sickness-like reactions, including chills, fever, edema, arthralgia and prostration. Severe and often fatal anaphylaxis has been reported. (See "Warnings.")

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Procaine toxicity manifestations have been reported (see "Warnings"). Procaine hypersensitivity reactions have not been reported with this drug.

Dosage and Administration: Administer only by *deep intramuscular injection,* in upper outer quadrant of buttock. In infants and small children, midlateral aspect of thigh may be preferable. When doses are repeated, vary injection site. Before injection, aspirate to be sure needle bevel is not in blood vessel. If blood appears, remove needle and inject in another site.

Although some isolates of *Neisseria gonorrhoeae* have decreased susceptibility to penicillin, this resistance is relative, not absolute, and penicillin in large doses remains the drug of choice. Physicians are cautioned not to use less than recommended doses.

Gonorrheal infections (uncomplicated)—Men or Women: 4.8 million units intramuscularly divided into at least two doses and injected at different sites at one visit, together with 1 gram of oral probenecid, given just before injection.

NOTE: Treatment of severe complications of gonorrhea should be individualized using large amounts of short-acting penicillin. Gonorrheal endocarditis should be treated intensively with aqueous penicillin G. Prophylactic or epidemiologic treatment for gonorrhea (male and female) is accomplished with same treatment schedules as for uncomplicated gonorrhea.

Retreatment: The National Center for Disease Control, Venereal Disease Branch, U.S. Dept. H.E.W. recommends:

Test cure procedures at approximately 7-14 days after therapy. In the male, a gram-stained smear is adequate if positive; otherwise, a culture specimen should be obtained from the anterior urethra. In the female, culture specimens should be obtained from both the endocervical and anal canal sites.

Retreatment in males is indicated if urethral discharge persists 3 or more days following initial therapy and smear or culture remains positive. Follow-up treatment consists of 4.8 million units aqueous penicillin G procaine, I.M. divided in 2 injection sites at single visit.

In uncomplicated gonorrhea in the female, retreatment is indicated if follow-up cervical or rectal cultures remain positive for *N. gonorrhoeae.* Follow-up treatment consists of 4.8 million units aqueous penicillin G procaine daily on 2 successive days.

Syphilis: all gonorrhea patients should have a serologic test for syphilis at the time of diagnosis. Patients with gonorrhea who also have syphilis should be given additional treatment appropriate to the stage of syphilis.

Composition: Each disposable syringe 2,400,000 units (4-ml. size) contains penicillin G procaine in a stabilized aqueous suspension with sodium citrate buffer, and as w/v approximately 0.5% lecithin, 0.5% carboxymethylcellulose, 0.5% povidone, 0.1% methylparaben, and 0.01% propylparaben. The multiple-dose 10-ml. vial contains per ml. 300,000 units penicillin G procaine in a stabilized aqueous suspension with sodium citrate buffer and approximately 7 mg. lecithin, 2 mg. carboxymethylcellulose, 3 mg. povidone, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben, and 0.14 mg. propylparaben.

Five are graduating with honors. How many with VD?

On the average, you can figure the incidence of VD among teenagers at about 900 per 100,000 population.* And growing.

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In the long run, a populace educated to the risks and prevention of VD is probably the best answer to the problem. Meanwhile, though, adequate doses of the recommended types of penicillin remain a formidable weapon.

IN SYPHILIS
INJECTION
Bicillin® L-A
(STERILE PENICILLIN G BENZATHINE SUSPENSION) WYETH

Syphilis is preferably treated with penicillin G benzathine, which is also the drug of choice for prophylaxis after exposure. Administration of 2.4 million units (1.2 million in each buttock) usually cures most cases of primary, secondary and latent syphilis with negative spinal fluid.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular penicillin G benzathine.—Venereal infections: Syphilis, yaws, bejel and pinta.

For deep intramuscular injection only.

Contraindication: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens.

Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms including fungi. Take appropriate measures should superinfection occur.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness-like reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high doses of parenteral penicillin.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Dosage and Administration: Venereal infections—

Syphilis—Primary, secondary and latent—2.4 million units (1 dose).

Late (tertiary and neurosyphilis)—2.4 million units at 7 day intervals for three doses.

Congenital—under 2 years of age, 50,000 units/Kg. body weight; ages 2-12 years, adjust dosage based on adult dosage schedule.

(Shake multiple-dose vial vigorously before withdrawing the desired dose.) Administer by **deep intramuscular injection** in the upper outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site. Before injecting the dose, aspirate to be sure needle bevel is not in a blood vessel. If blood appears, remove the needle and inject in another site.

Composition: Units penicillin G benzathine (as active ingredient): 2,400,000 units in 4-ml. single dose disposable syringe. Each disposable syringe also contains in aqueous suspension with sodium citrate buffer, as w/v approximately 0.5% lecithin, 0.6% carboxymethylcellulose, 0.6% povidone, 0.1% methylparaben, and 0.01% propylparaben. 300,000 units per ml.—10-ml. multi-dose vial. Each ml. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. povidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben, and 0.14 mg. propylparaben.

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*U.S. Dept. of Health, Education, and Welfare: VD Fact Sheet 1972. Publication No. (HSM) 73-8195

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Refer to: Pace JB, Nagle D: Piriform syndrome. West J Med 124: 435-439, Jun 1976

THE WESTERN
Journal of Medicine

Piriform Syndrome

J. BLAIR PACE, MD, *and* DENNIS NAGLE, MD, *Irvine*

Among a variety of deep muscle trigger points, the piriform muscle trigger point is selected for individual scrutiny. This seems fully justified by the great potential for confusing this entity with discogenic disease and consequently having unnecessary surgical procedures carried out.

The diagnosis can be made from findings on simple physical diagnostic tests and an appropriate history. Low back and hip pain with pain radiating down the back of the leg should suggest piriform syndrome as part of the differential diagnosis. This is especially true if a female patient has complaint of dyspareunia.

Pain and weakness on resisted abduction-external rotation of the thigh is a sign of piriform syndrome. This is confirmed by tenderness and reproduction of the patient's complaints by digital pressure over the belly of the piriform muscle, completing the diagnostic criteria.

Local injection of the muscle belly is curative. There are no laboratory or x-ray findings leading to a diagnosis.

IN DAILY PRACTICE, pain syndromes—including muscle trigger points[1]—due to focal hyperirritability of tissues are a common occurrence. To a patient they are real, disabling, distressing and, in fact, may dominate a person's very existence.[2] Diagnosis depends on a searching history and an examination by a physician who is experienced in identifying the telltale tender trigger points. Relief of pain by simple local injection is diagnostic proof.

A sound experimental basis for this phenomenon of focal hyperirritability of deep muscle tissue was developed years ago by Kellgren and Lewis[3] and reaffirmed by, among others, Inman and Saunders[4] of the University of California, San Francisco.

More recently, in the German literature a pathological lesion has been consistently identified in the muscle consisting of edema plus platelet aggregation.[5,6]

A particular deep muscle trigger point is singled out for report here because of the relative seriousness of the disability produced and because of the implications of misdiagnosis. This condition might best be called piriform syndrome. The term "piriformitis" as used in the German literature is rejected.[7] There is no sound evidence that the muscle trigger point syndromes are inflammatory.

From the Department of Family Medicine, University of California, Irvine, California College of Medicine; and the Problem Back Service, Rancho Los Amigos Hospital, Downey.

Submitted August 13, 1975.

Reprint requests to: J. Blair Pace, MD, Coordinator, Residency Programs, Department of Family Medicine, University of California, Irvine, California College of Medicine, 101 City Drive South, Orange, CA 92668.

Definition

Piriform syndrome is a clinical syndrome characterized by pain and disability. A description of the pain's location by a patient is often imprecise, the pain variously being considered a pain in the hip, tailbone, buttock or groin, and often down the back of the leg as sciatica. In females dyspareunia is often present and in both sexes there may be a limp, with dragging of the lower leg on the affected side.

Yoemans first described the syndrome in 1924,[8] and his description was expanded by Freiberg. Freiberg noted a test using forced internal rotation of the hip to show the presence of pain in the piriform muscle.[9,10] Proctologists discovered and frequently encountered pain and tenderness in the piriform muscle as part of the spectrum of causes of coccydynia.[11] Thiele found that pain radiated down the posterior thigh in the piriform syndrome. His concept of the pathophysiology was that muscle spasm and hypertrophy irritated the sciatic nerve. Thiele refers to 37 cases of piriform muscle pain. Shordania also reported on 37 cases all in women and termed the condition "piriformitis."

Incidence

The present report covers 45 cases gleaned from the practice of the senior author, primarily patients referred to the Problem Back Service at Rancho Los Amigos Hospital. The list is incomplete inasmuch as there was no standard coding for piriform muscle on our diagnostic index. The 45 cases are from some 750 patients admitted and processed through the Back Service. The ratio of females to males is 6 to 1. While the overall incidence may seem low, it is higher than confirmed incidence of disc protrusion with nerve root deficit in this group of referred patients.

Causes

There is no discernible common causative factor in piriform muscle syndrome. Trauma, or history of trauma is elicited in approximately half the cases. The nature of trauma is seldom dramatic. For example, it might be recounted by a patient as "My foot slipped as I ran around the swimming pool, but I caught myself and didn't fall." One man was spreading his knees to maximum while lowering one end of a large container between his knees and onto the floor. One lady suffered piriform syndrome as an occupational hazard. She worked long hours each day as a masseuse at a spa, always throwing the weight of her body to her right and over the client while checking with the hip abductors. One young woman developed a piriform syndrome after a fall while mountain climbing.

Early writers on this subject were impressed with the origin of the piriform muscle from the anterior capsule of the sacroiliac joint and felt that the syndrome was a result of sacroiliac arthritis.

We have seen severe tenderness of the piriform muscle in arthritis of the hip joint and a case of piriform syndrome subsequent to total hip replacement responded to simple local injection.

In spinal stenosis there may be bilateral piriform muscle tenderness not relieved by local injection.

Anatomy and Physiology

The piriform muscle arises from inside the pelvis, over the sacrum and anterior capsule of the sacroiliac joint. It runs laterally through the sciatic notch to become tendinous and insert on the greater trochanter of the femur. The belly of the muscle crosses over the sciatic nerve. In 15 percent of cases it has two bellies and the sciatic nerve runs between the two, or the nerve may have two trunks interdigitating with the two muscle bellies.

On physical examination, through rectum or

Figure 1.—The patient is told to push the hands apart with the knees. Weakness, faltering and a reproduction of pain on the left are present.

vagina, the piriform muscle belly lies above, that is, proximal to, the ischial spine and superior to the spino coccygeus ligament.

Along with the gemelli, the piriform is an external rotator, abductor of the thigh. In cases of piriform syndrome, the senior author has for several years described to students and residents a useful sign: weakness and pain on resisted abduction, external rotation of the thighs.[12]

Diagnosis

The diagnosis of piriform syndrome must be entirely clinical. The history may give clues, especially if one inquires about dyspareunia in female patients. Sometimes the nature of the trauma is highly suggestive, especially a history of almost falling but regaining balance.

It must be emphasized repeatedly that there are no x-ray or laboratory findings in this syndrome. Incidental x-ray reports showing "narrowing of the disc space" or "degenerative changes with spur formation" must not be taken as diagnostic of another condition.

Degenerative changes occur in the spine with aging and do not correlate well with symptoms.

On physical examination, one may find excellent range of motion of the lumbar spine despite the severity of symptoms. Patients may bend forward and touch the toes with knees extended. On the other hand, there may be restricted straight leg raising. There will almost invariably be sciatic notch tenderness on the involved side.

Physicians should examine searchingly. If a patient's pain is accepted and cooperation is obtained by the reassurance that the intent is quite literally to put the finger on the source of the pain, the patient will usually offer full cooperation. The usual routine back examination is carried out, including determination of the range of motion of back and of hips. Pain on internal rotation of the hips on the affected side is a positive Freiberg sign.[10]

A more consistent finding in piriform syndrome is that of pain and weakness on resisted abduction-external rotation of the thigh. This has not been previously reported in the literature. It simply tests for loss of function of the piriform muscle. With the patient seated, the examiner places his hands on the lateral aspects of the knees and asks the patient to push the hands apart. Faltering, pain and weakness will be observed on the affected side (Figure 1).

Rectal or pelvic examination, or both, should be *included in all* evaluations of low back complaints. In a patient with piriform syndrome, there will be distinct tenderness on the lateral pelvic wall which reproduces the original complaint. This tender trigger point is high—proximal to the ischial spine. The piriform muscle may seem tense or enlarged, or both. The patient manifests pain and often exclaims that for the first time someone has found "my pain."

Differential Diagnosis

Piriform syndrome is one of a number of conditions that may produce low back or pelvic pain with sciatica.[13,14] As such, it is most likely to be confused with herniated intervertebral disc. The two should be distinguished by lack of neurologic deficit in piriform syndrome. A diagnosis of discogenic disease should include neurologic deficit or evidence of nerve root tethering.

Facet syndrome with low back pain and sciatica may be difficult to diagnose unless one is willing to use differential therapeutic trials, injecting alternately the lumbar and lumbosacral facet joints.

When pelvic wall tenderness is bilateral, one may suspect spinal stenosis. This is especially true in patients in whom multiple surgical operations on the back have been carried out. We have, however, seen three cases in which there were

Figure 2.—Tray set up for injection into piriform muscle. **Upper left,** Kenalog 10 mg/cc, Xylocaine 1 percent, lubricant. **Lower,** sterile gloves, #22 spinal needle and two 6 cc syringes.

symptoms and findings that responded to piriform injection.

In patients in whom coccydynia and pain down the posterior thigh are present there may be muscle trigger points in other muscles—such as the gemelli, the quadratus femoris or obturatorius internus. Ischiogluteal bursitis, or weaver's bottom, is a similar pain. This condition is more likely to occur in victims of gout.

The differential diagnosis is made largely by precise palpation, physical examination and test of function. Pain and weakness on resisted external rotation is characteristic of piriform syndrome. On pelvic examination. the one muscle trigger point to be found proximal to the ischial spine is the piriform. The tendon of the piriform muscle is usually tender as it exits the sciatic notch.

Therapy

As in other deep muscle trigger point problems, the essential therapy is the injection of local anesthetic into the precise focal point of hyperirritability deep in the belly of the muscle.[12] Temporary local anesthesia reverses the hyperirritable state in the muscle.

One may, and usually does, add a small dose of corticoid to the second half of the local injection (see Figure 2). This does not imply that inflammation is responsible for muscle trigger point pain. Empirically, results are slightly more lasting and permanent with the addition of corticoid (10 mg of sterile triamcinolone acetonide suspension [Kenalog®] is usual for the author).

Figure 3.—Finger of left hand is on the tender spot. Spinal needle is aimed at the finger and can be felt to disturb tissues over the finger. Six ml of 1 percent Xylocaine is injected. Patient has relief. After waiting five minutes to detect possible injection into the sciatic nerve, a second injection is made. Second syringe contains 4 ml Xylocaine and 2 ml (20 mg) Kenalog.

TABLE 1.—*Summary of Previous Therapy and Incidence of Recurrence after Injection into Piriform Muscle*

	Patients	
	Female, 39	*Male, 6*
Bilateral piriform injections	3	..
Previous laminectomy	15	3
Laminectomy plus fusion	3	1
Facet block and/or caudal	13	2
Repeat piriform injection	4	..

A gynecologist may feel more comfortable making the local injection into the piriform by the vaginal route. An anesthesiologist may prefer going alongside the vagina to reach the piriform with a 3 inch spinal needle. The author has primarily trained orthopedic and family practice residents. Orthopedic residents seem to accept an approach through the sciatic notch just inferior to the bony margin. It is essential that the physician have one finger, or two, in the vagina or rectum and be palpating the precise tender spot in the muscle belly. The spinal needle is then aimed at the examining finger which can detect the needle disturbing the tissues under the examining finger.

The patient is awake and would let it be known if the needle touches the sciatic nerve. The needle should be proximal to the nerve. The first injection is clear 1 percent lidocaine (Xylocaine®). *No solids* are injected until a five minute period of observation notes pain relief on the part of the patient without numbness of the leg. The second syringe contains a mixture of 1 percent Xylocaine with corticoid (see Figure 3).

One correspondent reports treating the piriform muscle trigger point successfully by a special transvaginal ultrasonic applicator.

Results

We have reviewed the records of treatment of 39 female patients and six male patients. As in all our chronic pain patients, we find these patients' total complaints and disability to be multifactorial. Psychic stress, physical trauma, defensive need for pain, conversion hysteria, depression, facet syndrome and postoperative scar-

ring have all been observed in patients with piriform syndrome. In several, multiple surgical operations had been done before admission.

The usual routine allows for muscle trigger point injection as part of the examination and workup by the medical chief. More complex procedures may be scheduled to follow. The benefit and relief from piriform injection is immediate and dramatic. The patient literally discards the crutches and walks away without limp.

Several patients had had facet block done before piriform block (see Table 1). The facet block may relieve the back pain, but only piriform block relieves the limp and buttock, posterior thigh pain.

Of 39 female patients, bilateral injections were done in three. In one male patient treated with injection there was relief of pain after a full six weeks of inpatient treatment at our facility without relief. In this latter case, all our usual measures had failed. The patient had very strong psychological predictors for failure; however, improvement after piriform block was sustained.

Recurrences are uncommon. A patient, mentioned previously, who worked as a masseuse had a recurrence, related to her occupation, and chose to retire. One patient from the author's private practice had two recurrences in 20 years. A woman, 40 years old, had a mild relapse after three weeks and was reinjected with relief that has now lasted for one year.

Duration of symptoms before diagnosis and injection is often quite long, indicating a lack of knowledge among physicians generally. We have seen patients in whom symptoms have been present for from six months to four years. One young woman was diagnosed and successfully treated two months after she slipped while mountain climbing.

Complications

We have noted no complications with this method of treatment. The question most frequently asked is "aren't you afraid of hitting the sciatic nerve?" The patient is awake and will tell you if you touch the nerve. It would be possible to produce a footdrop if one injected solid material, such as suspended corticoid, into the nerve. To prevent this, we use a double syringe technique.

In summary, it is well to emphasize that local injection of muscle trigger points is both diagnostic and therapeutic. There are no laboratory or x-ray findings that are useful in making a diagnosis. One must rely entirely on clinical acumen.

The condition discussed, piriform syndrome, is one of a number of conditions that may give rise to "sciatica." This list includes facet syndrome discogenic disease, ischiogluteal bursitis and perhaps others. Disability from piriform syndrome is very lasting and severe even though true neurologic deficit should never be found. One should be alert to the condition and include function testing and pelvic examination in all low back and hip or thigh pain complaints.

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Tuberculous Enteritis

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Tuberculous enteritis occurs in about 2 percent of patients with pulmonary tuberculosis. Although it is uncommon in the United States, tuberculous enteritis should be considered in any patient with active pulmonary tuberculosis and abdominal complaints.

Eight cases of T. enteritis have been treated at Harbor General Hospital in the last 25 years. Associated pulmonary disease was shown radiologically to be present in seven of eight patients. Findings on contrast studies of the gastrointestinal tract showed disease in six of six patients examined.

In five patients, surgical operation was required for diagnosis or complications. Resection of diseased bowel with primary anastomosis was done in five patients. Although medical therapy is the mainstay in the treatment of both pulmonary and intestinal tuberculosis, one staged resection of diseased bowel with primary anastomosis is the procedure of choice for complications such as obstruction, hemorrhage or perforation.

TUBERCULOSIS OF THE intestinal tract is uncommon in the United States. The fact that the disease occurs infrequently results in diagnostic oversight. We report eight cases of tuberculous enteritis treated at Harbor General Hospital in the last 25 years, five since 1964. Emphasis is placed on early diagnosis and surgical management of complications. Current concepts in the clinical management of gastrointestinal tuberculosis are reviewed.

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Materials and Methods

All cases in which there was histopathologic or radiographic evidence of tuberculous gastrointestinal disease in combination with positive acid-fast bacillus smears of cultures are included in the study.

Table 1 lists the patients' chief complaints, as well as initial hemogram and radiographic findings in these cases. No patient gave a history of contact with tuberculosis. On physical examination, a tender right lower quadrant mass and fever were noted in half of the patients. Rales were reported on examination of the chest in only one patient.

Results

One patient died before effective therapy was initiated. Another patient was treated successfully with isonicotinic acid hydriazide (Isoniazid®) and ethambutal hydrochloride (Myambutal®) alone.

In five patients, surgical operation was carried out for diagnosis or treatment of a complication. The correct preoperative diagnosis was made in only one patient (see report of case). Resection of the diseased bowel was done in four of the five cases in which operations were carried out; extensive disease in the fifth precluded resection. Two of the five patients died of the disease shortly after operation while the remaining three were well at last follow-up.

Pathologic findings are shown in Table 2. Three of the eight patients died from overwhelming tuberculosis. The five survivors were all well and asymptomatic at the time of their last clinic visit. Morbidity in the survivors was limited to confinement for adequate treatment of pulmonary disease.

In all, there was microbiologic evidence of infection with mycobacterium tuberculosis in seven of the eight patients (Table 3).

TABLE 1.—*Chief Complaint and Initial Diagnostic Studies*

Patient	*Age, Sex*	*Race*	*Symptoms*	*X-ray Findings*	*Hemogram*
1 ..	76 ♀	B	Abdominal pain, rectal bleeding	CXR—No active pulmonary disease BE—Irritable colon and cecal volvulus	PCV—36% WBC—11,700
2 ..	69 ♂	C	Abdominal pain	CXR—Consistent with pulmonary tuberculosis	PCV—36% WBC—9,000
3 ..	73 ♂	C	Abdominal pain, constipation	CXR—Consistent with pulmonary tuberculosis	PCV—45% WBC—10,800
4 ..	72 ♂	A	Abdominal pain, weight loss	CXR—Consistent with pulmonary tuberculosis BE—Cecal obliteration and narrowing of terminal ileum	PCV—32% WBC—9,900
5 ..	26 ♀	C	Abdominal pain, chronic cough, fever	CXR—Far advanced pulmonary tuberculosis BE—Cecal obliteration UGI's—Stricture of terminal ileum	PCV—43% WBC—6,600
6 ..	45 ♂	C	Fever, cough, weight loss	CXR—Advanced pulmonary tuberculosis with cavitation BE—Cecal mass and multiple strictures of right colon	PCV—38% WBC—7,500
7 ..	12 ♂	C	Abdominal pain, weight loss	CXR—Calcified primary complex BE—Right colonic stricture with dilated proximal colon and terminal ileum	PCV—21% WBC—3,200
8 ..	58 ♂	C	Weakness, weight loss	CXR—Advanced pulmonary tuberculosis with cavitation UGI's—Gastric ulcer, ulcerated terminal ileum, cecal mass and fistula	PCV—34% WBC—4,300

CXR = x-ray film of chest
BE = barium enema
PCV = packed cell volume (hematocrit)
UGI = upper gastrointestinal series
WBC = leukocyte (white blood cell) count

TABLE 2.—*Treatment, Pathology and Results*

Patient	*Operation*	*Pathology*	*Hospital Stay (days)*	*Mortality*
1 ..	Exploratory laparotomy	Widely disseminated tuberculosis, tuberculous enterocolitis, retroperitoneal abscess, caseation necrosis	16	+
2 ..	None	Pulmonary tuberculosis, tuberculous enteritis with caseation necrosis	6	+
3 ..	Parital distal ileal resection with primary anastomosis	Acute inflammatory infiltrate with necroses and perforation of distal ileum secondary to tuberculous enteritis	1	+
4 ..	None	None	152	−
5 ..	Right hemicolectomy and primary ileo-transverse colostomy	Fibrous adhesions (operation and pathologic findings at another hospital)	121	−
6 ..	Resection of terminal ileum and right hemicolectomy with primary ileo-transverse colostomy	Tuberculous entercolitis, caseation necrosis	104	−
7 ..	Right hemicolectomy and primary ileo-transverse colostomy	Tuberculous enterocolitis with partial cecal obstruction, caseation necrosis	26	−
8 ..	Ileo-right hemicolectomy with primary jejuno-transverse	Tuberculous enterocolitis with three free perforations, caseation necrosis	125	−

TABLE 3.—*Microbiologic Data*

Patient	*Smear*	*Positive Culture*	*Organism*
1	+neck sinus; −peritoneal fluid	Sputum	Mycobacterium tuberculosis
2	.....	Sputum	Mycobacterium tuberculosis
3	.....	.....	.....
4	+gastric washing	Sputum	Mycobacterium tuberculosis
5	+sputum	Sputum	Mycobacterium tuberculosis
6	+sputum	Sputum; gastric washing	Mycobacterium tuberculosis
7	.....	Resected bowel	Mycobacterium tuberculosis
8	+ gastric washing; + sputum	Sputum; gastric washing	Mycobacterium tuberculosis

Report of a Case

The complication of free perforation has occasionally been noted to occur during treatment with antituberculous drugs.[1] The patient discussed below is an example of such a case.

A 55-year-old white man (listed as patient number 8 in tables) was admitted to Harbor General Hospital in August, 1972 with complaint of weakness, melenotic stools and a 23-pound weight loss over a ten-week period. Medical history included symptoms of peptic ulcer, and a gastric ulcer had been documented on a previous gastrointestinal series. The patient had a 40 pack per year smoking history but had no knowledge of tuberculosis contacts.

Temperature on admission was 38°C (101°F) and other vital signs were normal. On physical examination, atelectatic pulmonary rales and dif-

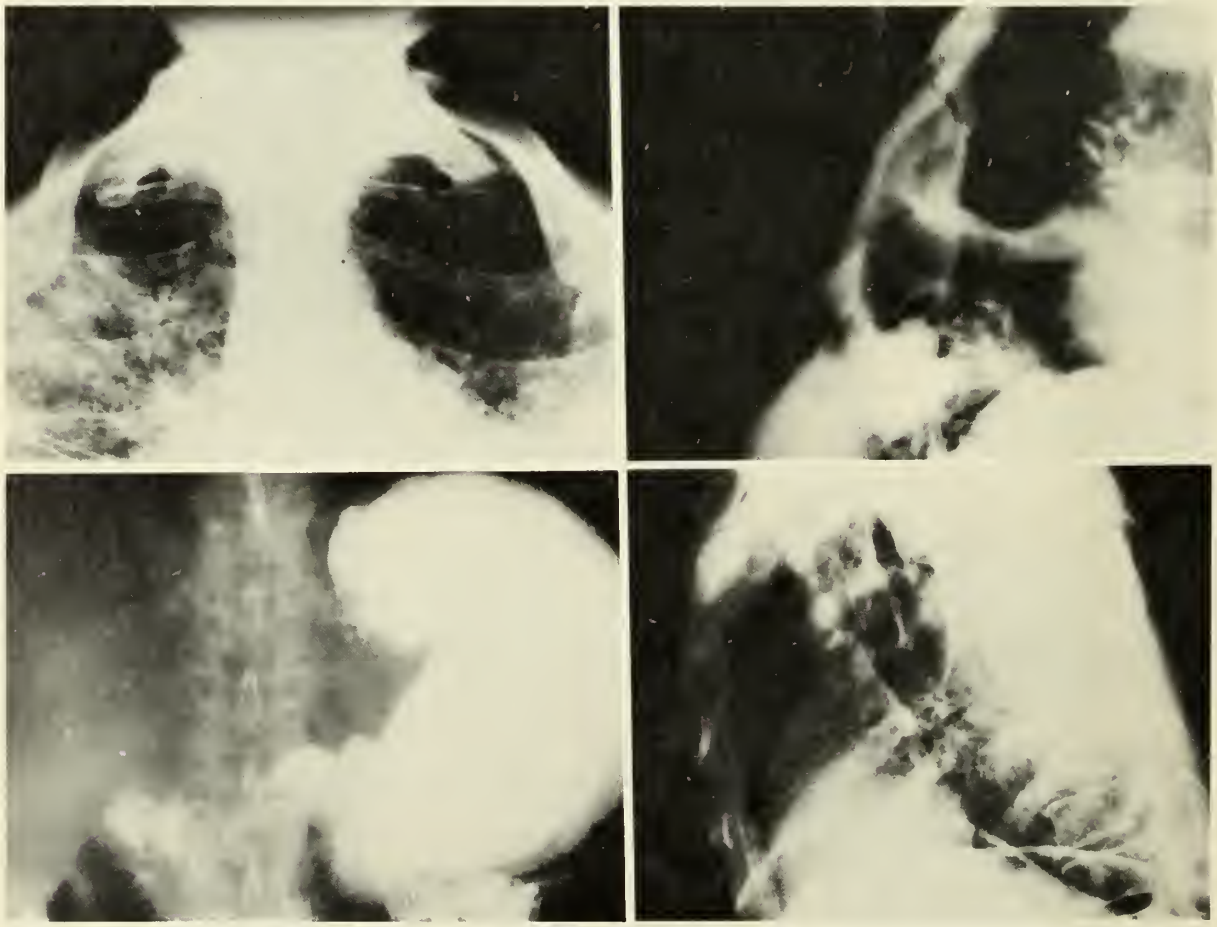

Figure 1.—Upper Left, initial chest film; **Lower Left,** upper gastrointestinal series; **Upper Right,** small bowel follow-through; **Lower Right,** lateral chest film.

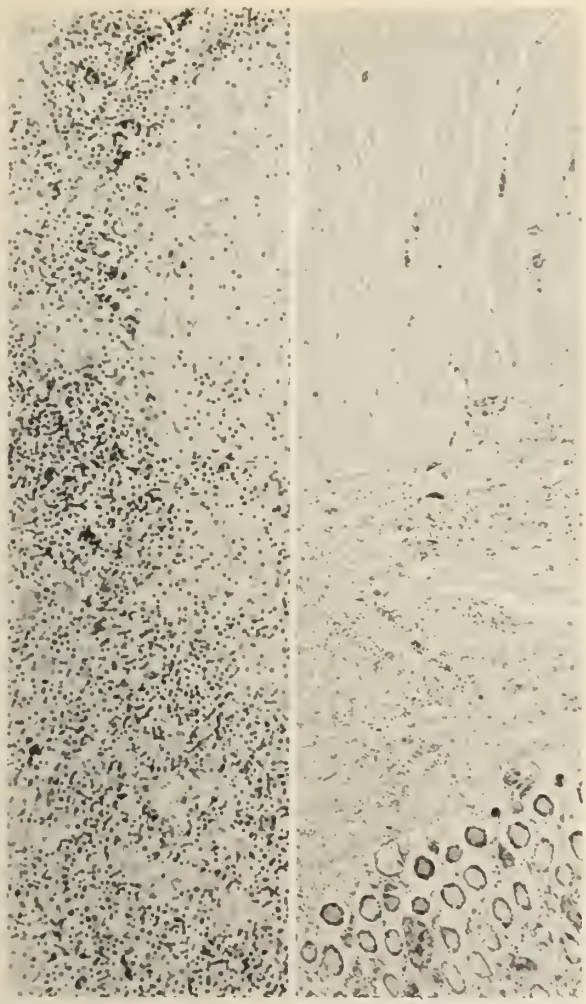

Figure 2.—Left, mesenteric lymph node with multinucleated giant cells—reduced from 40×Mag.; **Right,** ileum with caseated submucosal tubercles—reduced from 10×Mag.

fuse abdominal tenderness were noted. Admitting laboratory study findings included an hematocrit of 34 percent, leukocyte count of 4,300 and normal serum electrolytes. Bilateral cavitary upper lobe infiltrates were identified on an x-ray film of the chest (Figure 1). Findings on further diagnostic studies included a positive reaction to intradermal injection of 100 Todd units of purified protein derivative (second-strength PPD), and a positive acid-fast smear of gastric washings. A diagnosis of pulmonary tuberculosis was made and antituberculous therapy begun with isonicotinic acid hydriazide (Isoniazid®) and ethambutol hydrochloride (Myambutol®).

On upper gastrointestinal series a gastric ulcer was noted, and small bowel follow-through showed ileal mucosal ulceration and compression of the cecum by an extrinsic mass (Figure 1). These findings were felt to be consistent with tuberculous enteritis.

After ten days of treatment, acute abdominal pain developed suddenly. Based on x-ray evidence of free peritoneal air (Figure 1), a perforation of the previously noted gastric ulcer was suspected and the patient was taken to surgery. At the time of operation, three free perforations of the distal ileum were identified in association with severe tuberculous peritonitis. The gastric ulcer had not perforated. The involved ileum and right colon were resected and a jejuno-transverse colostomy carried out. Examination of the gross specimen showed fibrosis and mucosal ulceration typical of tuberculous enteritis, and histopathologic examination showed caseation necrosis although tubercle bacilli were not identified (Figure 2).

Following operation the patient did well but a lengthy hospital stay was required for treatment of pulmonary lesions. Subsequent gastroscopic examination showed there to be complete healing of the gastric ulcer. When last seen, 18 months after discharge, the patient was asymptomatic and working actively as a longshoreman.

Discussion

Tuberculous enteritis is uncommon in the United States. The low incidence of the primary form is undoubtedly due to rigid control of dairy herds and pasteurization of milk. To our knowledge, primary gastrointestinal tuberculosis has not been reported in this country since 1964.

In 1930, Brown and Sampson felt intestinal tuberculosis to be the most common extrapulmonary manifestation of pulmonary tuberculosis.[2] Almost 70 percent of patients dying from pulmonary tuberculosis in that era had tuberculous enteritis.[3-5] More recent studies indicate that in cases of early pulmonary tuberculosis there is a 1 percent incidence of tuberculous enteritis, while in advanced cases the incidence has been reported as high as 70 to 80 percent.[6,7]

It is generally felt that gastrointestinal tuberculosis is caused by the ingestion of tubercle bacilli and consequent invasion of the mucosa by the organism.[8,9] The most common site of intestinal disease is the ileocecal area which is involved in about 90 percent of all cases.[2,10] Localization here is due to stasis of well-digested intestinal contents in an area of active absorption.[11,12] Other sites of intestinal involvement in order of decreasing

frequency are the jejunum, appendix, sigmoid colon, rectum, duodenum, stomach and esophagus.[12] Generally accepted pathologic criteria for making the diagnosis of tuberculous enteritis include the histologic demonstration of tubercle bacilli in the lesion, the histologic evidence of tubercles with caseation necrosis or an accurate gross description of operative findings with biopsies of nodes which show evidence of caseation necrosis.

The rarity, variability and absence of a pathognomonic test frequently obscure the diagnosis of tuberculous enteritis. Age is not a particularly helpful differentiating factor although the average age of our patients, 56 years, would support the reports of others in noting a higher incidence in older patients.

Symptomatology is quite variable. Abdominal pain, as in our series, is the most consistent complaint; followed by fever, weight loss, diarrhea and symptoms of intestinal obstruction. Symptoms in our patients generally followed this pattern, although diarrhea was not reported.

While findings on physical examination may be suggestive, they obviously are not sufficient evidence to confirm the diagnosis of tuberculous enteritis. An abdominal mass is reported in more than 70 percent of cases of tuberculous enteritis and we found a mass in 50 percent of our patients. Results of examination of the abdomen that are consistent with an acute condition within the abdomen or intestinal obstruction are not unusual but characteristically suggest more common causes for these problems.

Although routine gastrointestinal contrast studies in patients with pulmonary tuberculosis are unnecessary, gastrointestinal symptoms, weight loss or occult blood in the stool are indications for carrying out upper gastrointestinal series and barium enema. Because of the frequent occurrence of tuberculous enteritis in the ileocecal area, it may be impossible to distinguish colonic carcinoma or regional enteritis from gastrointestinal tuberculosis on contrast studies.

The inability to differentiate between carcinoma of the colon and tuberculous enteritis on radiographs is often an indication for operation. Coexistent colon carcinoma and tuberculous enteritis have been reported[14] and this must be borne in mind when operation is considered.

The findings on intestinal contrast studies in our patients, although consistent with tuberculous enteritis, were also interpreted to suggest Crohn's disease, toxic megacolon, perforated ulcer and carcinoma. Diagnosis was made from contrast studies in one patient when reexamination following antituberculous chemotherapy showed resolution of both pulmonary and intestinal lesions. Once diagnosed, uncomplicated tuberculous enteritis can be effectively treated with antituberculous drugs such as isonicotinic acid hydriazide and ethambutol hydrochloride.

The complications of tuberculous enteritis which may require surgical operation include hemorrhage, obstruction, perforation with abscess formation, free perforation and fistula formation. Obstruction is the most frequent complication and usually occurs late in the disease as inflammation subsides and fibrosis progresses. Failure of obstruction to resolve with nonoperative measures necessitates resection of the diseased bowel with primary anastomosis.

In cases of tuberculous enteritis, the incidence of perforation with associated abscess formation has been reported as high as 7 percent.[15,16] Free perforation, rare even before the use of antituberculous drugs,[17] has been reported in the literature only 18 times before 1960.[18] Since then we are aware of only four additional cases.[18-20] In three of the four cases the patients' recovery was satisfactory following operation. Because the finding of free air on x-ray films of the abdomen is most commonly associated with perforated peptic ulcer, the surgeon is generally surprised to find intestinal tuberculosis with free perforation.

Resection of the involved bowel with primary anastomosis in combination with antituberculous chemotherapy is now the recommended treatment for the surgical complications of tuberculous enteritis.[21] Freant and Sawyers' review of the surgical management of tuberculous enteritis concludes that resection of the diseased bowel with primary anastomosis is the safest and most efficacious treatment.[22] In our five patients in whom operation was carried out, resection with primary anastomosis was utilized successfully in three.

The previously reported 50-percent operative mortality in perforated tuberculous enteritis[20] may be attributed to two factors. Firstly, infection with a combination of enteric organisms and tubercle bacilli results in a particularly virulent peritonitis. Second, in a debilitated patient with tuberculosis simple closure of the perforation is often ineffective because of poor wound healing and the frequent presence of distal intestinal stenosis results

in disruption of proximally sutured perforations. In our series the only operative mortality following resection occurred at 24 hours after operation when the patient died from overwhelming pulmonary infection.

Our results and the more recent experience of others lead us to recommend the inclusion of tuberculous enteritis in the differential diagnosis of patients with active pulmonary tuberculosis and abdominal pain. The antituberculous drugs, isonicotinic acid hydriazide (Isoniazid®), para-aminosalicylic acid (Pascorbic®) and ethambutol hydrochloride (Myambutol®) are the mainstays of therapy of both pulmonary and gastrointestinal tuberculosis. When complete obstruction, hemorrhage or perforation occur, we feel one-stage resection of the diseased bowel with primary anastomosis is the operation of choice.

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New Names in Oregon

THE UNIVERSITY OF OREGON HEALTH SCIENCES CENTER is the new name for what have been known individually as the University of Oregon Dental School, the University of Oregon Medical School and the University of Oregon School of Nursing. Consolidation of the three schools occurred November 22, 1974. Along with the new status as a Health Sciences Center has come authority for the UOHSC to act for the Oregon State Board of Higher Education in granting degrees to its own students. Previous to the Northwest Association of Schools and Colleges approval of the UOHSC as a "candidate for accreditation" in March of 1975, authority to award degrees rested in the University of Oregon.

The former Multnomah Hospital and Medical School Hospital have been newly licensed as *University Hospital* as of March 1976.

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Medical PROGRESS

Refer to: Odell WD, Swerdloff RS: Male hypogonadism (Medical Progress). West J Med 124:446-475, Jun 1976

Male Hypogonadism

W. D. ODELL, MD, PhD, *and* R. S. SWERDLOFF, MD, *Torrance*

NORMAL REPRODUCTIVE and sexual function in males requires the integrated activities of a number of anatomical areas or organ systems, which when combined make up the reproductive axis. For simplicity, we have divided these components into (1) the extrahypothalamic central nervous system, (2) hypothalamus, (3) pituitary gland, (4) the testes (both Leydig cell and spermatogenic tubules) and (5) the many tissues that are responsive to the hormonal effects of gonadal steroids. More detailed evaluation would show that each of these has in turn subcomponent endocrine, neuronal or biochemical systems. Abnormalities of any of these components may result in clinically apparent reproductive dysfunction. Such dysfunction may become manifest at different times in a patient's life: (1) during embryogenesis, resulting in abnormal sexual differentation of genitalia; (2) before sexual maturation, resulting in failure to attain adult secondary sexual characteristics and reproductive capacity, and (3) after puberty, resulting in a decline in normal sexual and reproductive function. Therefore, an understanding of male reproductive dysfunction requires consideration of both the embryological development of male genitalia and the reproductive hormonal axis.

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The Reproductive Hormonal Axis

The hypothalamic-pituitary-testicular axis is a complex interlocking system, through which modulating effects, occurring at a number of organ or anatomical levels, result in the maintenance of appropriate concentrations of gonadal steroids, and in the regulation of spermatogenesis. We have represented this system by the simplified scheme depicted in Figure 1.

The Extrahypothalamic Central Nervous System

From studies in experimental animals it is apparent that extrahypothalamic brain tissue has both augmentary and inhibitory influences on reproductive function. Sawyer[1] has recently completed an excellent review on the role of the amygdala in reproductive function. These studies reveal that estrogen receptors exist in the amygdala in rabbits and rats, and that both facilitory and inhibitory influences modify hypothalamic-pituitary-gonadotropin function. Furthermore, sensory systems, such as olfaction, and light have important roles as modifiers of reproductive processes in rodents and nonhuman primates. For example, the odor of a strange male mouse will interrupt early pregnancy in a female by blocking prolactin secretion (Bruce effect). The same odor will coordinate estrus cycles in nonpregnant female mice (Whitten effect). (See excellent review by Bronson.[2]) These are examples of the effects of pheromones or semiochemicals. Michael[3]

ABBREVIATIONS USED IN TEXT

A = androstenedione
ACTH = adrenocorticotropic hormone
AMP = adenosine monophosphate
ATP = adenosine triphosphate
3β-HSD = 3β-hydroxysteroid dehydrogenase
DHA = dehydroepiandrosterone
DHT = dihydrotestosterone
DNA = deoxyribonucleic acid
DOC = desoxycorticosterone
E_1 = estrone
E_2 = estradiol
FSH = follicle-stimulating hormone
FSH-RH = FSH releasing hormone
GnRH = gonadotropin releasing hormone (also called LRH and LH-FSH RH)
HCG = human chorionic gonadotropin
LH = luteinizing hormone
LH-FSH RH = luteinizing-follicle-stimulating hormone releasing hormone (also called GnRH and LRH)
LRH = luteinizing hormone releasing hormone (also called GnRH and LH-FSH RH)
RNA = ribonucleic acid
SHBG = sex hormone binding globulin
T = testosterone
TRH = thyrotropin-releasing hormone
TSH = thyroid-stimulating hormone

has recently reviewed his excellent studies indicating these pheromones also play a role in primate reproduction. Female rhesus monkeys elaborate such chemicals in vaginal secretions which act as male attractants. When placed on the perineum of a castrate female, these chemicals induce excitement and attraction in males. In addition, human females also elaborate chemically similar substances in vaginal secretions; amounts vary with stage of the menstrual cycle as they do in monkeys. It is not known whether these act as sex attractants in humans, but when the human vaginal pheromone is applied to the castrate female monkey, its effect is as dramatic as, and is indistinguishable from, the original monkey pheromone. In addition, light affects reproductive function in female and male rodents. As early as 1932, Bissonnette[4] noted that female ferrets could be brought into heat during the normal anestrum by prolonging exposure to light. In addition, estrus could be terminated during the breeding season by covering the eyes or blinding. The effect of light varies from species to species. In sheep, estrus is induced by increasing darkness.[5] Everett and associates in 1949[6] were able to obtain precise estrus cycles in rats by precisely controlling light. In addition, *constant light* has been shown to produce precocious puberty in female rats.[7] Fewer studies have been done in males because of difficulties in accurately determining onset of sexual maturation. Bissonnette[4,8] showed that in male ferrets there was increased testis size and earlier mating when day length was increased. In blind girls, Zacharias and Wurtman[9] have reported that menarche occurs earlier than in normally sighted girls. (The effects of light are opposite in rats and humans. This is attributed to the fact that rodents are nocturnal animals; humans are not.) Similar studies have not been done in boys, but blind men do not appear to have abnormal night-day patterns of blood, luteinizing hormone (LH), follicle-stimulating hormone (FSH) or gonadal steroids.[10] Evidence that higher cortical function may influence the hypothalamic reproduction includes the frequent occurrence of menstrual abnormalities in emotionally stressed women, and studies showing depressed serum testosterone levels in mentally stressed men.[11] The role of extrahypothalamic brain function on the pulsatile release of hypothalamic and pituitary hormones (see below) remains an area requiring further research.

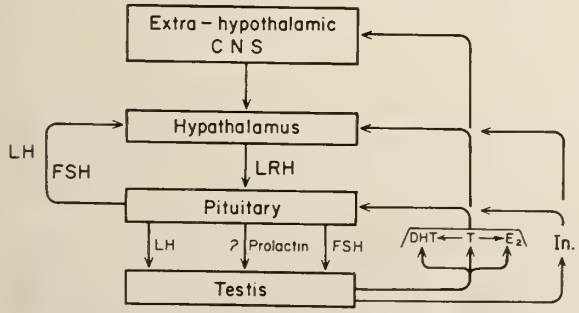


Figure 1.—Schematic representation of the closed-loop feedback of the central nervous system-pituitary-testicular axis.

The Hypothalamus

The hypothalamus represents the important integrative center in the reproductive axis. It is at this level that both neural messages from the central nervous system, and at least part of the humoral messages from the testes, act to modulate the secretion of hypothalamic gonadotropin releasing hormone (GnRH) and thereby gonadotropin secretion. Studies in animals indicate that the hypothalamus may be further subdivided into areas involved in positive (stimulatory) feedback

and negative (inhibitory) feedback. In rats the preoptic-suprachiasmatic area has been named the cyclic area by Barraclough and Gorski,[12] and is responsible for triggering the LH-FSH ovulatory surge that causes ovulation. More medial in the rat, in the arcuate-ventromedial area, is the so-called tonic center, involved in relaying cyclic center data into GnRH* secretion, and also in direct or inhibitory feedback control by gonadal steroids. Much of the experimental evidence concerning these concepts has been published by Pfeiffer[13] and Barraclough;[12] Barraclough and Gorski showed that small doses of testosterone administered to female rats within a few days of birth would result in nonfertile, noncycling animals after sexual maturity. No effect was produced in males; the testosterone secreted at birth by normal prepubertal testes produced the same effect in males as the injected testosterone did to females. (Small doses of estrogens also produce such effects. It has been postulated by Naftolin and associates[14] that testosterone acts by first being aromatized to estradiol within hypothalamic tissues. Dihydrotestosterone, an androgen that is not converted to estrogen, does not produce "androgen sterilization." This is discussed in more detail later.) Before Barraclough's studies, Pfeiffer[13] had shown that if a male rat were castrated at birth and an ovary transplanted after sexual maturity, cyclic function and ovulation from the transplanted ovary occurred. If the ovary were transplanted into a male castrated at maturity instead of neonatally, cyclic function did not occur. Additional data from many laboratories, using lesioning and stimulation studies, localized the two areas to the anatomic areas discussed earlier, in rats, mice and probably rabbits. At present, it is presumed that such areas exist in humans, but no certain data exist. Odell and Swerdloff[15] showed that sequential estrogen-progestogen treatment in castrate or postmenopausal women produces ovulatory surges, but could not show such surges in castrate (as adults) men or eugonadal men. Recently, Zarazet and co-workers[16] showed that estrogen-progestogen treatment in men with testicular feminization produces ovulatory surges. Such men, because of a defect in androgen action at a cellular level, have not been exposed to the action of androgens. Further studies of such phenomena in men castrate or agonadal since birth need to be made. It is commonly presumed, therefore, that in eugonadal men there is little or limited ability for positive feedback phenomena, while such phenomena occur typically in eugonadal women. Further studies determining the presence or absence of such phenomena in congenitally hypogonadal men may help to clarify the cause for this physiological sex difference.

In addition to these considerations of the internal portions of the hypothalamus, it also appears that neurotransmittor substances, probably biogenic amines, are involved in relay of data from the cyclic to the tonic area and possibly the secretion of GnRH. Because alterations in cyclic function are more easily detected than alterations in testicular steroid secretion or spermatogenesis, most studies assessing the role of biogenic amines on reproductive function have been carried out in females. In animals, the effects of norepinephrine, serotonin or dopamine are varied depending upon the circumstances and possibly route of administration. Thus, we prefer not to attempt to construct a detailed scheme at this time. (Recent reviews have been written by McCann and associates,[17] Weiner and associates[18] and Frohman.[19])

Hypothalamic modulation of pituitary secretion

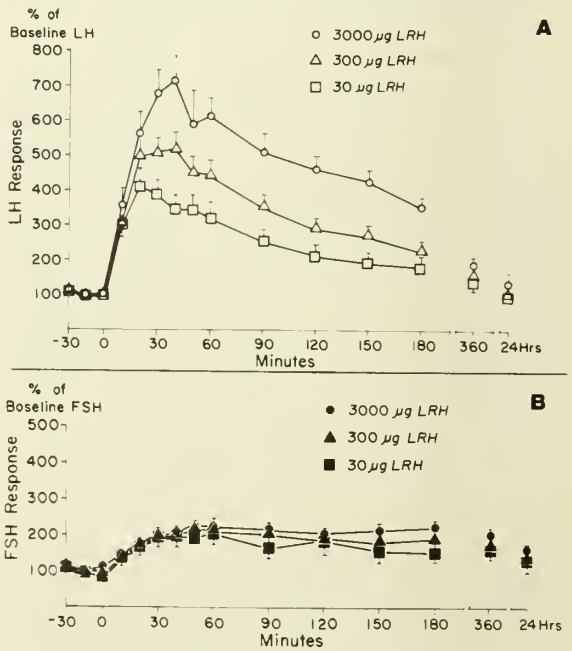


Figure 2.—Response of a group of eugonadal men to three doses of luteinizing hormone releasing hormone (LRH) given as an intravenous bolus at time zero. Brackets enclose one SEM. **A**, luteinizing hormone (LH) response, **B**, follicle-stimulating hormone (FSH) response. (Reproduced with permission from Wollesen F, Swerdloff RS, Odell WD[40])

*Gonadotropin releasing hormone is also called luteinizing hormone releasing hormone (LRH) or luteinizing-follicle-stimulating hormone releasing hormone (LH-FSH RH).

of luteinizing hormone and follicle stimulating hormone is mediated by means of a decapeptide hormone secreted into the pituitary portal vascular system.[20,21] Gonadotropin releasing hormone (GnRH) has now been synthesized and widely used for research and clinical purposes, and has been identified in the hypothalamus of humans[22] and in the hypophyseal portal blood of other species.[23,24] However, attempts to measure this substance in the peripheral blood of animals or humans has been fraught with problems. Bioassays using large amounts of peripheral blood have been done,[25] but these do not lend themselves easily to dynamic testing; the radioimmunoassays currently available appear to be of borderline sensitivity and are adversely affected by nonspecific substances in the serum or plasma of man.[26-28] These problems will undoubtedly be overcome in the near future, but for the present clinically reliable measurements of GnRH are not available. The effects of GnRH on the secretion of LH and FSH by the human pituitary gland have been amply studied. In adult humans, GnRH is a potent stimulator of LH release, but only a weak stimulator of FSH secretion[29-40] (see Figure 2). In prepubertal children, however, GnRH has a greater effect on FSH.[30] However, the fact that GnRH predominantly modifies LH secretion, coupled with the observation that in many clinical and physiological circumstances, elevations in FSH may be greater than that of LH,* has led some investigators to speculate on the presence of a second FSH releasing hormone (FSH-RH). While findings from earlier animal studies suggested the presence of such a substance,[41-44] recent attempts to isolate and purify a separate FSH-RH have not been successful. It is most commonly believed that the action of GnRH on the pituitary results from modulation of pituitary response by testicular steroids and other feedback substances. However, recent studies in women from our laboratory shed considerable doubt on this.[45]

The Pituitary Gland

The pituitary gland is the site of synthesis and release of gonadotropic hormones. The two major hormones in humans are identical in both sexes and are commonly named after their effects in the female. Luteinizing hormone and follicle stimulating hormone are glycopeptides that consist of two separate peptide chains (α and β).[46-51] The alpha chain is identical for both hormones while the chemically unique beta chains provide biologic specificity to the molecules. The function of the carbohydrate portions is uncertain, but it is likely that one important role is protection from biologic degradation.[52]

LH and FSH are secreted into the general circulation and act on the testes to mature and maintain reproductive capacity. The metabolic clearance rate of LH is considerably greater than that of FSH, resulting in more rapid disappearance from the circulation of LH compared with FSH. Both hormones are secreted in an episodic fashion by the pituitary, but the longer survival of FSH in the circulation is reflected by more constant serum levels of that hormone than that of the more rapidly metabolized luteinizing hormone. These episodic secretions result in fluctuations of FSH and LH which may be ±100 percent of the average (Figure 3). In addition to these short-term fluctuations, Rubin and co-workers[56] have shown that LH, but not FSH, has changes correlated with Stage I and II of sleep, but such changes are small. Other than these sleep related studies, diurnal variations in LH and FSH secretion do not appear to occur in adult men. (See Odell and Moyer[57] for review.) Interestingly, Boyar and co-workers[58] have shown that LH and possibly FSH increase in blood in children during puberty. However, this sleep induced secretion largely disappears in sexually mature men and women. While LH and FSH are the major gona-

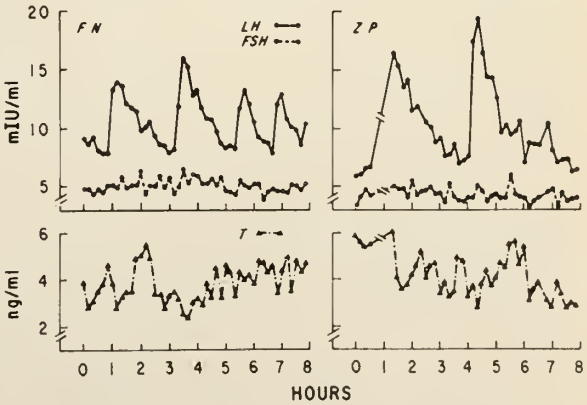


Figure 3.—Changes in testosterone (T), luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in two eugonadal male subjects when samples are obtained each few minutes. (Reproduced with permission of author and publisher from Naftolin F, et al[55])

*Using the International Reference Preparation for LH and FSH (IRP-HMG #2), blood FSH is greater than LH in castrate men or women, in postmenopausal women, at the first half of the follicular phase of the menstrual cycle and in men with selective testicular tubule dysfunction; while LH is greater than FSH during the ovulatory surge and after LRH administration to eugonadal men and women.

dotropic hormones we consider in humans, other pituitary hormones may have effects on the testes. For example, in male rats prolactin has been shown to have synergistic effects with LH on testosterone secretion by the testes.[59,60]

The Testis

The testis consists of two major components: (1) the spermatogenic tubules, which in adults represent 80 to 90 percent of the testis mass, and (2) the Leydig cells, which are found in clusters in the interstitial tissue surrounding the spermatogenic tubules.

Leydig cell function. The Leydig cells are the primary source of testosterone and more than 95 percent of the testosterone produced in normal men is from testicular secretion. Laatikainen and associates[61] have shown that testosterone sulfate is directly secreted by testes; spermatic vein concentration ranged from less than 1 to 3.9 μg per 100 ml. The testes also secrete Δ^4 androstenedione and dehydroepiandrosterone; relative concentrations in spermatic vein blood are 2.9 μg per 100 ml (testosterone), 4.5 μg per 100 ml (Δ^4 androstenedione) and 47.9 μg per 100 ml (dehydroepiandrosterone).[62] Smaller amounts of dihydrotestosterone—and the potent estrogen, estradiol—are secreted. The biochemical pathways of testicular steroidogenesis are presented in Figure 4. Luteinizing hormone stimulates steroidogenesis by enhancing the conversion of cholesterol to pregnenolone. This biochemical effect involves a series of related steps: (1) binding of LH to receptors on cell membrane, (2) activation of the enzyme, adenyl cyclase, with conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (AMP), (3) conversion of inactive protein kinase to active protein kinase and (4) activation or synthesis of enzymatic proteins resulting in increased steroidal biosynthesis.

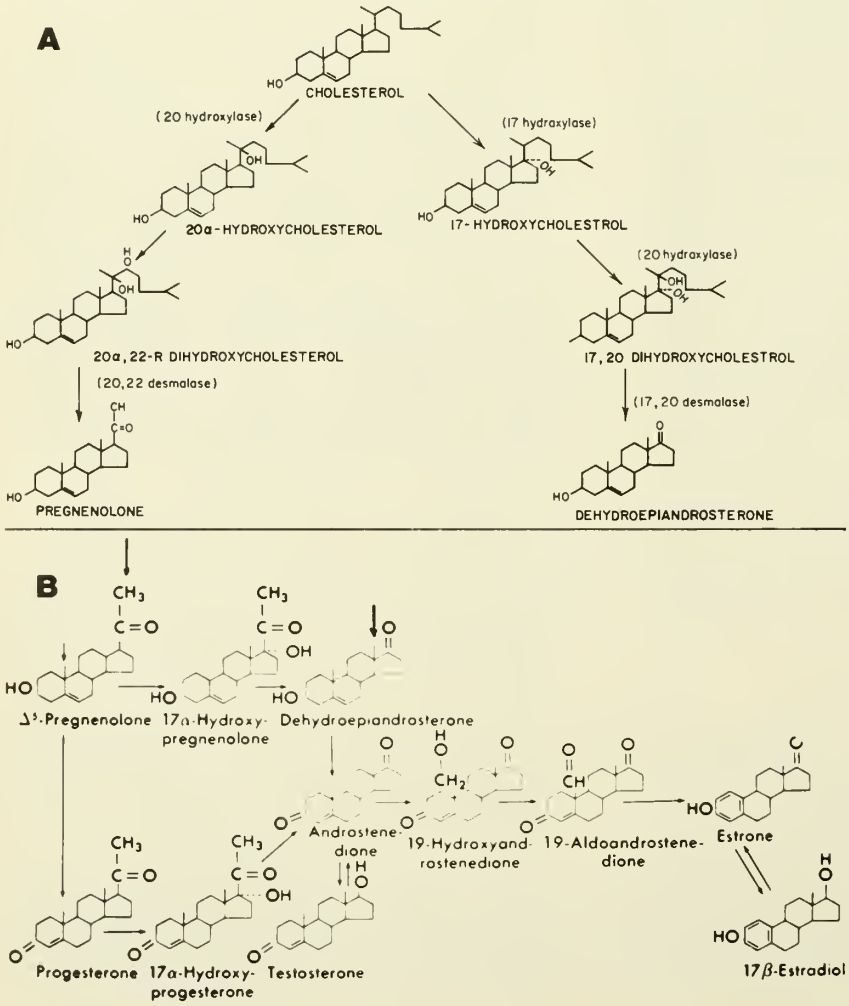


Figure 4.—A, enzymatic pathways for conversion of cholesterol to pregnenolone or dehydroepiandrosterone to enter the androgen synthesis pathways. Subsequent pathways beyond pregnenolone and dehydroepiandrosterone are shown in Figure 4B (Modified from Kirkland RT, et al[63]). **B**, enzymatic pathways for conversion of pregnenolone or dehydroepiandrosterone or testosterone and estradiol (Modified from Odell WD, Moyer DL[57]).

Circulation of Gonadal Steroids in Blood

Testosterone (T) and estradiol (E_2) both circulate in blood predominantly bound to a beta globulin known as testosterone-estrogen binding globulin or sex hormone binding globulin (SHBG); smaller amounts are bound to other proteins, such as an inter-alpha globulin and albumin.[64,65] Only a small fraction of the total serum testosterone and estradiol circulates in an unbound form. It is the small unbound concentrations of T and E_2 that are responsible for the biologic activity of the hormones. Figure 3 shows the serum concentrations of serum LH and testosterone in a normal adult male in whom blood samples were obtained at frequent time intervals.[55] These pulsatile LH changes occur throughout the day in adult men and are superimposed upon slower poorly predictable changes occurring at night. There is a nocturnal elevation in blood testosterone not explainable by LH, FSH or prolactin concentration[56] and not related to changes in metabolic clearance. In addition to these two causes for change in testosterone concentrations, concentrations also change with body position and exercise. Such changes may be explained by alterations in hepatic clearance of testosterone.[66] The relationship between the short-term, rapid episodic changes in serum T and LH are also subject to some controversy. Naftolin and co-workers[67] and Rubin and co-workers[68] have observed episodic rises in serum LH that precede the rises in serum T. Rubin and associates,[68] using computer analysis of multiple samples collected during sleep, found small but positive correlations of both serum LH and prolactin levels with T secretion. The latter authors have suggested that nighttime elevations in serum prolactin concentrations may act synergistically with circulating LH to cause the nocturnal rise in serum T.

Peripheral Conversion of Steroids

The three major steroid hormones acting in feedback control of the hypothalamic-pituitary-testicular axis are testosterone, dihydrotestosterone and estradiol. As indicated earlier, in eugonadal men more than 95 percent of circulating testosterone is derived from testicular secretion.[69,70] Obviously, this percentage may be altered in various hypogonadal states. The sources of dihydrotestosterone (DHT) and estradiol are complex and are schematically depicted in Figures 5 and 6. Dihydrotestosterone is both directly secreted by the testes and formed in peripheral tissues by conversion from testosterone. In some bioassays, DHT is more potent (about two times) than testosterone, and thus, its role in feedback control could be significant. DHT, of course, is also formed directly from testosterone in some target tissues. As will be discussed later, this may be an obligatory step for androgen effects on some tissues. Estradiol also is formed by direct secretion and by peripheral conversion from testosterone. Longcope and associates[72] have estimated

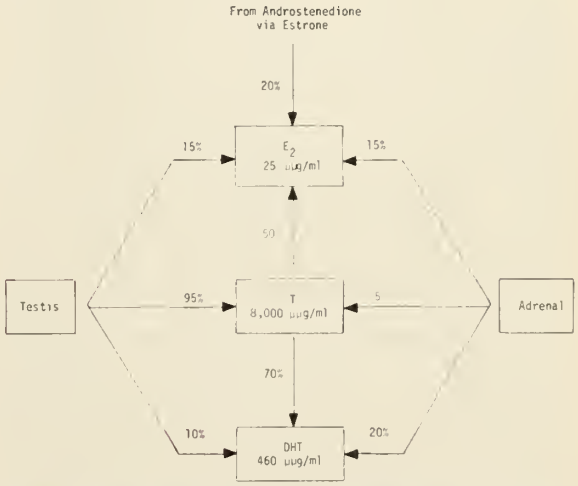


Figure 5.—Estimated sources of testosterone (T) and dihydrotestosterone (DHT) in eugonadal men. The relative amount of directly secreted androstenedione and dihydrotestosterone secreted by the adrenal and testis are approximate. E_2 = estradiol, $\mu\mu$g = micro microgram (picogram, pg).

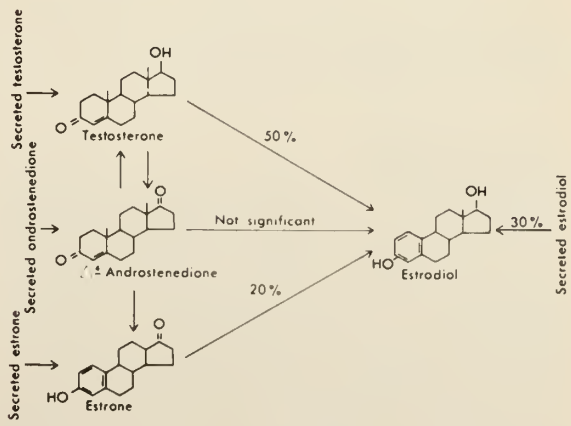


Figure 6.—Sources of blood estradiol estimated from data of Longcope C, Kato T, Horton R.[72] (Reproduced with permission of the publisher from Odell WD, Moyer DL[67])

that only about 30 percent of the circulating estradiol is derived from glandular secretion, and 70 percent is formed by peripheral conversion. MacDonald and co-workers[73] disagree with this, and believe 100 percent of the estradiol could be derived from peripheral conversion. Measurements of arterial-venous estradiol gradients in spermatic vessels[74-76] would indicate that direct secretion does occur (see Figures 5 and 6).

Control of Leydig Cell Function

The control of Leydig cell secretion is believed to result primarily from actions of LH. Administration of human chorionic gonadotropin (an "LH-like hormone") to prepubertal boys or normal men or LH to various animals produces increases in blood testosterone, and treatment of normal men with exogenous testosterone (or estradiol) for two to five days lowers blood LH concentrations.[66,77,78] However, this is not the entire story, other hormones modify LH action on testosterone secretion. Odell and co-workers[60,79-81] have shown that immature male rats, five days after hypophysectomy, become very poorly responsive to LH. Treatment with purified FSH restores responsiveness to LH, and the magnitude of the LH stimulation of testosterone production appears related to the duration of exposure to, as well as the amount of, FSH. These workers have hypothesized that FSH induction of *responsiveness to* LH is a major mechanism of sexual maturation.[60,80] In addition, Johnson and Ewing[82] have shown in isolated, perfused rabbit testes, that FSH acts synergistically with LH to stimulate testosterone secretion.

In addition to FSH modification of LH responsiveness, as was indicated earlier, prolactin may also modify the testicular response to LH stimulation of testosterone secretion.[59]

Spermatogenesis

The transformation of spermatogonia to mature spermatozoa is normally controlled by actions of both LH and FSH. Lostroh[83] showed that once spermatogenesis had *regressed* after hypophysectomy of the rat, both LH and FSH were required to initiate the process, and to produce mature sperm. In seeming conflict, Nelson[84] showed that if testosterone treatments were given, beginning the day of hypophysectomy, spermatogenesis could be *maintained* indefinitely in the absence of LH and FSH. Walsh and Swerdloff[85] showed there to be a biphasic response of administered testosterone on spermatogenesis in eugonadal rats. Low doses of testosterone inhibited serum LH, FSH and spermatogenesis, while high doses of testosterone maintained spermatogenesis despite suppressed serum LH and FSH levels. Recently, Vonberswordt-Wallrabe and Mehring[86] showed that in adult rats, after complete regression of spermatogenesis has occurred following hypophysectomy, very large doses of testosterone will restore spermatogenesis, and full fertility can subsequently be maintained indefinitely. These exciting findings have led to the hypothesis that FSH acts to change the tubule permeability to testosterone or to production of a testosterone binding protein, the end result of which is increased testosterone concentrations within the tubule; testosterone per se stimulates spermatogenesis. LH acts to stimulate Leydig cell production of testosterone. According to our extension of this hypothesis, FSH would act during puberty to permit testosterone concentrations to increase locally, at testosterone secretory rates, which would not excessively stimulate sex accessories in young boys. This hypothesis could explain why Short[87] detected mature sperm in urine of boys that were only at Stage I to II of puberty.

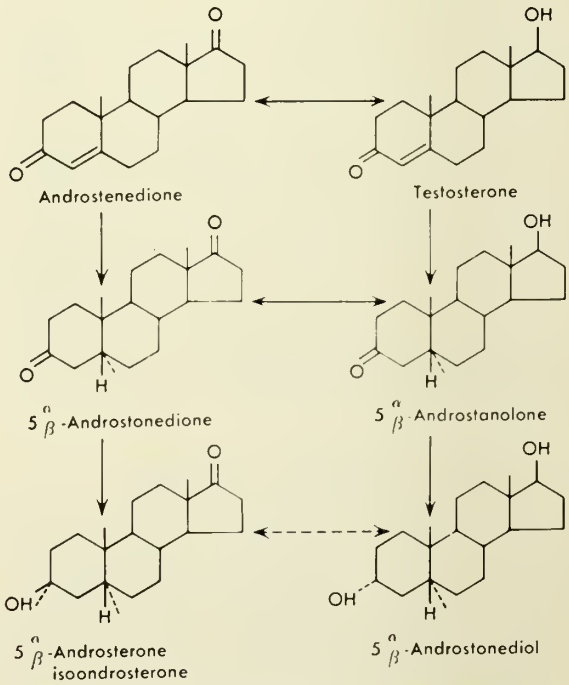


Figure 7.—Metabolic pathways for testosterone degradation in the human. (Reproduced with permission of the author and publisher from Mauvais-Jarvis P et al[88])

Degradation of Testosterone

Degradation of testosterone occurs predominantly by two pathways in the liver in man (see Figure 7). One pathway involves the oxidation of the 17β-hydroxyl group to form androstenedione. Androstenedione is further reduced to a 5α and 5β androstanedione and then to androsterone, isoandrosterone and 5α and 5β androstanediol. The last three substances are excreted as sulfates and glucuronides. A second pathway involves a direct reduction of testosterone by specific Δ^4-3-ketosteroid, 5α and 5β reductases, and a specific 3-hydroxysteroid dehydrogenase, to form 5α and 5β androstanediols, which are glucuroconjugated.

Actions of Testosterone

Testosterone, the predominant circulating androgen in males, produces a variety of effects on hormone-sensitive body tissues. These effects include the growth and maturation of the prostate, seminal vesicles, penis and scrotum; the development of male hair distribution, such as beard, pubic, chest and axillary hair; laryngeal enlargement and vocal cord thickening. Testosterone stimulated protein synthesis results in increased muscle mass and strength in men compared with women. Behavioral changes, such as increased aggressiveness, and enhanced sexual drive are testosterone augmented responses. The role of testosterone in sex organ development of the fetus is described later.

Normal Sexual Organ Development

Normal male sexual development consists of three sequential processes: (1) genetic sex development, which is determined at the time of fertilization of the ovum (normal male sex chromosome complement is 46 XY); (2) gonadal differentiation, which is the process by which the indifferent gonad develops into the testis or ovary (the steps by which the genetic information determines this process are unknown), and (3) phenotypic sexual development, the process which transforms the internal and external sex organ anlage into the sex specific form.

The internal genitalia arise from the wolffian and müllerian ducts that exist side by side in the early embryo. Differentiation of the ductal systems into the male internal genitalia occurs under the influence of two fetal hormones. (The definition of a hormone varies among endocrinologists. Strictly speaking this substance is produced locally and acts locally and does not fit the usual definition of a hormone; that is, produced by one tissue.) In males, the wolffian ducts give rise to the seminal vesicles, vas deferens and epididymis. Wolffian duct differentiation requires the presence of adequate local concentrations of testosterone produced by the testes. In females, the müllerian ducts give rise to the upper vagina, uterus and fallopian tubes. Regression of the müllerian ducts, which requires the presence of a separate testicular hormonal substance, normally occurs in the male fetus preventing the development of female internal organs. Josso[89,90] has partially characterized the embryonic testicular substance responsible for müllerian regression; it appears to be a peptide with a molecular weight of greater than 15,000. Table 1 summarizes the hormonal control of the development of sex accessories and genitalia.

The external genitalia in both sexes arise from common anlage: the genital tubercle, urogenital sinus, genital folds and swellings. The genital tubercle gives rise to the glans penis in the male and clitoris in the female. The urogenital sinus is the origin of the prostate, and prostatic urethra in the male and the lower two-thirds of the vagina, and urethra in the female. The genital folds become the labia minora of the female, but fuse to become the penile shaft in the male. The urogenital swellings give rise to the female labia majora or fuse to form the male scrotum. For excellent reviews see Grumbach and Van Wyk[91] and Jost.[92] In the absence of a testis, the external genitalia develop along female lines. In the male, testosterone is secreted by the fetal testis and converted in the urogenital tract by enzymatic reduction to dihydrotestosterone (see below). It is the latter hormone that is responsible for the conversion of undifferentiated anlage of the external genitalia into the male form.[93,94] Therefore, fetal testosterone induces masculinization of the male genitalia by acting directly on the

TABLE 1.—*Hormonal Control of Male Sexual Differentiation in Man*

Testis secretes
Testosterone
Müllerian regression factor
Testosterone acts
Directly to initiate virilization of wolffian ducts producing male genitalia
As prohormone for dihydrotestosterone (DHT) that initiates virilization of anlage of external genitalia
Müllerian regression factor acts
To suppress müllerian duct development

wolffian ducts, but acts on the anlage of the external genitalia only after intracellular conversion to dihydrotestosterone occurs. Alterations in intracellular formation of dihydrotestosterone may result in varying degrees of feminization affecting only specific tissues requiring dihydrotestosterone action.

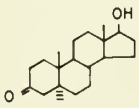
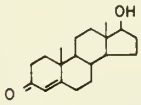
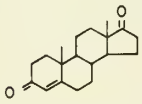
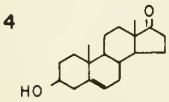
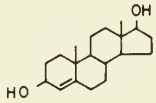
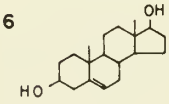
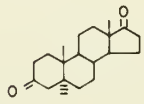
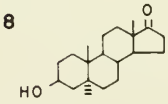
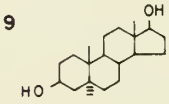
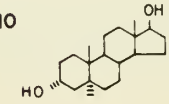
Mechanism of Action of Testosterone

In 1968, Bruchovsky and Wilson[95] showed that after intravenous injection of 3H-testosterone into rats, dihydrotestosterone could be recovered from prostatic tissue; this was the only testosterone metabolite present. Subsequently, Liao and Fang in 1969[96] showed that relatively high affinity receptor proteins exist for dihydrotestosterone within prostatic tissue. Grover and Udell[97] have shown recently that the receptors in the cytosol bind *both* testosterone and dihydrotestosterone, the former is bound about 30 percent as well as the latter. Biologically active androgens, other than testosterone or dihydrotestosterone, are either also bound to these receptor proteins—thus, initiating androgen action—or alternatively are converted *in vivo* after administration to testosterone or some other active androgen. Table 2 depicts some of these data. Therefore, the initial steps in testosterone action involve (1) binding to cytosol receptor proteins per se or conversion to dihydrotestosterone, and binding to cytosol receptor (depending upon the particular tissue), and (2) transport of the steroid-receptor complex to the nucleus.

Within the nucleus, the complex is bound to chromatin and initiates deoxyribonucleic acid (DNA) directed ribonucleic acid (RNA) mediated transcription events and the cellular changes related to androgen action[98,99] (Figure 8).

As was stated earlier, not all tissues convert testosterone to dihydrotestosterone for androgen action. In normal male rabbits, dihydrotestosterone formation is lower in the wolffian ducts of the fetus than in tissues derived from the wolffian ducts in adult males. This suggests the possibility that tissues derived from wolffian ducts (anlage of seminal vesicles, vas deferens and epididymus)

TABLE 2.—*Relative Androgen Potencies of Ten Steroids* In Vivo *(Prostate Weight Assay) and* In Vitro *(Prostate Cytosol Assay). Potency of Dihydrotestosterone (DHT) Was Defined as 100 Percent. (Reproduced with Permission of the Author and Publisher from Grover and Odell.*[97]*)*

	Steroid	In Vivo %	In Vitro %
1		100.0	100.0
2		37.0	33.0
3		15.0	not active
4		12.6	not active
5		46.0	12.7
6		7.4	12.7
7		12.2	6.6
8		0.74	not active
9		1.1	20.0
10		100.0	2.3

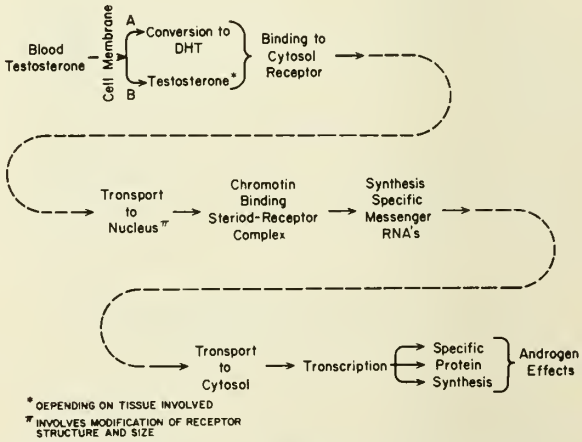


Figure 8.—Schematic presentation of the intracellular mechanism of action of testosterone. Note that alternate pathways exist (A and B). Depending on the tissue, testosterone may bind to cytosol receptor as testosterone, or testosterone may be converted to dihydrotestosterone (DHT) and bound to cytosol receptor.

acquire or notably increase their ability to convert testosterone to dihydrotestosterone (this is true in humans, guinea pigs and rabbits).[94] This is in contrast to nonwolffian duct tissue. There is also evidence to suggest that conversion to dihydrotestosterone is not involved in testosterone effects on sexual behavior. In fact, estrogens simulate the actions of testosterone on such behavior.[3] Naftolin and co-workers[14,100] have shown that testosterone is aromatized (A ring) to estradiol in hypothalamic tissue and have postulated that most or all of the effects of testosterone on the central nervous system require conversion to estradiol. The presence of estrogen receptors within the hypothalamus and other central nervous system tissues has been reported by several groups.[101-104] To date androgen receptors have been identified by one group.[105] The fact that various tissues respond to DHT, T or E_2 differently helps to explain some hypogonadal states where isolated tissues have failed to respond to androgens, while the person from whom the tissues were taken is otherwise a normal male (Type II male pseudohermaphroditism). Figure 8 presents schematically a postulated concept for testosterone action in males. Figure 9 presents a postulated scheme for the mediation of the metabolic actions of testosterone in different tissues. The last is highly conjectural, but offers an interesting hypothesis for further study.

Feedback Control

As depicted in Figure 1, the hypothalamic-pituitary-gonadal system consists of a closed-loop feedback control mechanism directed at maintaining normal reproductive function. In this system, gonadal hormones and their metabolic products have inhibitory effects on the secretion of LH and FSH. This is easily shown by the rise in serum LH and FSH seen after orchiectomy (Figure 10).[106] It is to be noted, from Figure 10, that LH and FSH rise very slowly but steadily after castration, reaching maximum possibly only after 25 to 50 weeks. This rather sluggish response is characteristic of the testicular system in men and in contrast to most of the endocrine systems. This phenomenon is also shown by the 48-hour in-

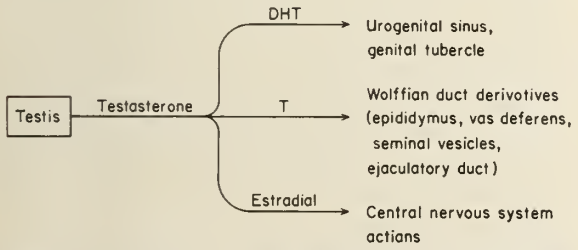


Figure 9.—Schematic presentation of the postulated routes of testosterone action in different tissue. DHT = dihydrotestosterone, T = testosterone.

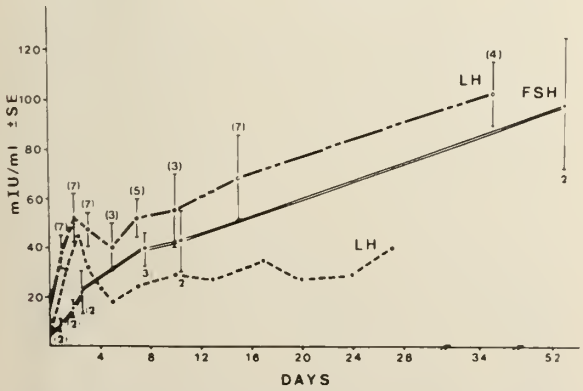


Figure 10.—Changes in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in eugonadal men after castration. Brackets enclose SEM. Numbers in parentheses indicate subject following subcapsular (presumably incomplete) orchiectomy. (Reproduced with permission of the author and publisher from Walsh P et al[106])

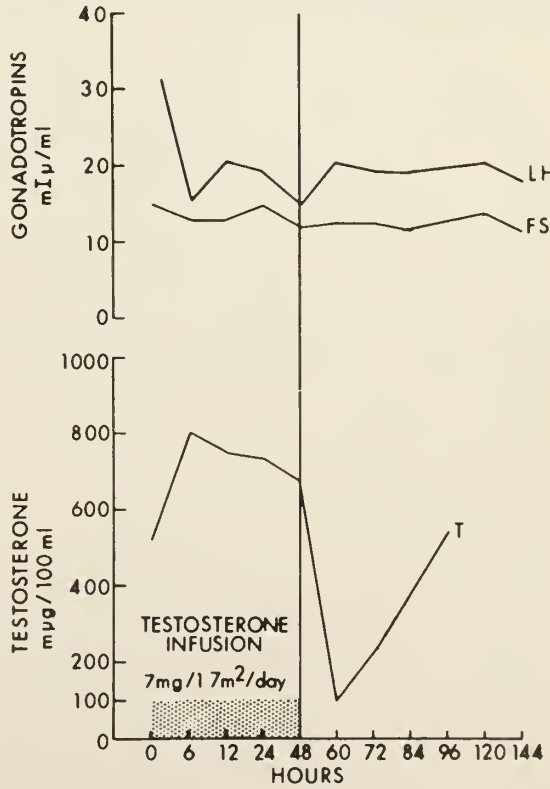


Figure 11.—Effects on blood luteinizing hormone (LH), follicle-stimulating hormone (FSH) and testosterone (T) concentrations of a 48-hour infusion of testosterone into an eugonadal man. (Reproduced with permission of the author and publisher from Stewart-Bentley M et al[78])

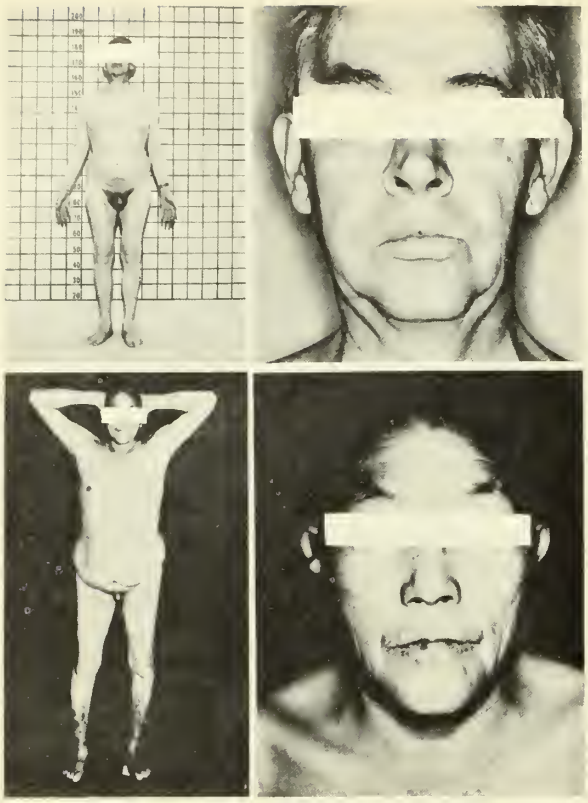


Figure 12.—Upper Left and Right, full body and face of a man with isolated luteinizing hormone (LH) and follicle-stimulating hormone (FSH) deficiency. Patient had a history of bilateral undescended testicles, made to descend with human chorionic gonadotropin treatment as a child. He had serum LH and FSH concentrations that were low to normal, no response to six days of clomiphene citrate (Clomid®) treatment. Plasma testosterone=163 μg per 100 ml (N=300 to 1,000 at our laboratory at this time). **Lower Left and Right,** full body and face of a man with Klinefelter's disease. He had been under care for diabetes mellitus for eight years before his hypogonadal facies and diminished body hair were noted and related to hypogonadism. He had karyotype of 47 XXY, serum LH=45 mIU/ml, and FSH=91 mIU/ml. Testosterone=250 mμg/ml.

fusion studies depicted in Figure 11. (It is interesting that the changes after castration of male rats occur much more rapidly than they do in men.) Dramatic and rapid inhibition of LH and FSH secretion is seldom seen during infusion of testosterone or estradiol to normal men.[78] Nevertheless, the complex of steroid hormones, depicted in Figure 1 (estradiol, testosterone and dihydrotestosterone), act in feedback control of LH and FSH secretion. Although the rate of peripheral conversion of testosterone to estradiol is very small and the resultant concentrations of blood estradiol small, estradiol is much more potent than testosterone in feedback suppression of LH and FSH (about a thousandfold). Therefore, blood estradiol may still contribute significantly to feedback control of LH and FSH—as could estradiol formed from testosterone *in situ* within the central nervous system. (For a recent review, see Odell WD, Swerdloff RS: Feedback control of pituitary gonadotropins, *In* Raspe G [Ed]: Advances in Biosciences [#15]. New York, NY, Pergamon Press, 1975, p 141). Feedback control of FSH is slightly more complex than that of LH; steroidal substances do not appear to be the only factors involved. Procedures that selectively decrease spermatic tubule function (such as low-dose ionization radiation,[107] chemotherapy[108] or experimental cryptorchidism[109]) result in moderately elevated blood FSH, and no changes in LH. The increases in blood FSH are *not* as high as those observed in castrate animals. Such observations support the suggestions made in 1923 by Mottram and Cramer,[110] and in 1932 by McCullagh,[111] that the germinal epithelium secretes a nonandrogenic, nonestrogenic water soluble substance called inhibin. Recently, Franchimont and others[112] developed a novel assay system for such a substance (that is, its inhibitory effects on the FSH release in response to luteinizing hormone releasing hormone [LRH]). Using this assay approach, Franchimont has isolated a peptide of molecular weight about 20,000 from bull semen. In simultaneous but independent studies, Baker and co-workers[113] in Australia have also shown the existence of a water soluble material that has FSH inhibiting effects.

CLINICAL PRESENTATION OF HYPOGONADISM

Hypogonadal Facies

The distribution of the facial beard in normally virilized males is dependent on the person's particular racial background. Deviations from that distribution may indicate the presence of hypogonadism. Normal beard distribution varies on one extreme: to cheek, moustache, chin and neck region requiring shaving once to twice daily; to the other extreme: mainly, chin and moustache hair requiring shaving once each one to two days. The former is "normal" for more hirsute Caucasian subraces; such as those of Mediterranean, Italian, Armenian and many French-English-Spanish extractions. The latter is normal for those of Oriental-Indian extraction. Therefore a beard distribution that is normal for a Japanese or Chinese man may be abnormal for a Caucasian. A detailed history of the "normal" hair distri-

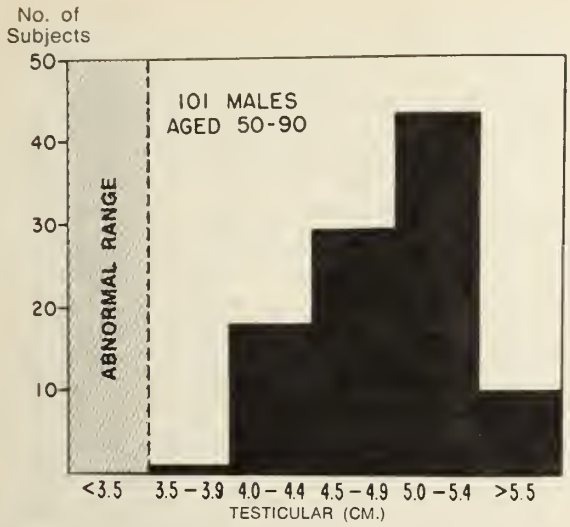


Figure 13.—Testicular size in 101 men in hospital who were more than 50 years old. (Reproduced with permission of author and publisher from Lubs HA[114])

bution in the family of the patient is worthwhile, and often shows there to be striking differences in the patient from his father and brothers.

As women undergo estrogen deprivation changes after menopause, the development of hypogonadal facies occurs. These are "normal" for postmenopausal women; the same changes occurring in men are abnormal and indicative of hypogonadism. (These facial changes in men occur *in addition* to alterations in beard distribution.) Typically, these changes, consisting of fine linear creases extending radially outward from the mouth and eyes, are finer than those produced by aging and also different than those allegedly produced by heavy smoking.

Consequently, in observing even a fully clothed man, an alert diagnostician can suspect hypogonadism by noting a beard distribution that is abnormal for racial background coupled with the hypogonadal changes about the mouth and eyes. Figure 12 depicts the face and body of two hypogonadal men.

Body Hair Distribution

Body hair distribution also varies with racial background. An Oriental typically has trunk hair limited to the sternal area, with axillary and pubic hair present in abundant amounts. It is unusual for Oriental-Indian racial subgroups to have trunk hair over the pectoral areas or over the back and flank; extremity hair is present, but is usually less than in the hirsute Caucasian subgroups. On the other extreme of normal, some hirsute Caucasion subgroups have long black hair distributed over the entire thorax including back, shoulders, and abdomen. Furthermore, axillary and pubic hair are extremely heavy; the former not limited to the apex, the latter extending in large amounts up to and even above the umibilicus. The finding of a pattern, normal for an Oriental, in a man from a hirsute Caucasian racial background may indicate decreased testosterone secretion and hypogonadism. Thus, it is important to assess familial and racial norms for body hair distribution.

Testicular Size

Approximately 90 percent of testicular volume is made up of spermatic tubules; the interstitial cells comprise the remaining small volume. Using an orchidometer or centimeter ruler to estimate testicular size is a necessary part of the physical examination. Figure 13 illustrates the frequency distribution of testicular length in men over age 50 from the publication of Lubs.[114] We consider testis less than 4 cm in length as being abnormal. It is important to note, however, that Leydig cell function may be normal in some testes that are smaller than 4 cm. In such a testis, tubular function would be expected to be subnormal.

ABNORMALITIES IN HYPOTHALAMIC-PITUITARY FUNCTION

Clinically recognizable hypogonadism in men in the presence of low blood levels (or low normal blood levels) of LH, low FSH, or both, implies a disturbance in hypothalamic-pituitary function. Such a disturbance may be part of a global anterior pituitary disturbance, panhypopituitarism, or of an isolated LH or FSH deficiency. It is usually not possible to distinguish isolated LH and FSH deficiency from panhypopituitarism clinically. Figure 12 shows the physical appearance of a man with LH-FSH deficiency and a testosterone level of 163 μg per 100 ml, illustrating the subtle findings that are occasionally extremely useful. Each of the syndromes will not be discussed separately here since they are separated for the most part based on repeated measurements of LH, FSH and testosterone. A normal XY karyotype is found in all patients in Category I of Table 3.

A common associated finding in Category I-B patients is anosmia or hyposmia. This finding on physical examination of a hypogonadal male is strong but not unequivocal evidence that a hy-

pothalamic disturbance is present. Males and Schneider[115] described a man with hypergonadotrophic hypogonadism and anosmia. It is not known whether this was chance occurrence or causally related.

Panhypopituitarism

Any mass lesion involving the hypothalamus or pituitary can interfere with all or selected pituitary hormone secretion. Any patient with hypogonadotropism should be adequately studied for ability to control and secrete each of the other pituitary hormones. Methods for assessing such functions are discussed later.

TABLE 3.—*Findings in Patients with Hypogonadism By Category*

- I. Abnormalities in Hypothalamic-Pituitary Function
  - Panhypopituitarism
  - Isolated luteinizing hormone (LH) and/or follicle-stimulating hormone (FSH) deficiency
  - LH-FSH deficiency
  - Isolated FSH deficiency
  - Isolated LH deficiency
  - Kallman's syndrome
  - Prader-Willi syndrome
  - Lawrence-Moon Biedl syndrome
  - Cerebellar ataxia
- II. Primary Gonadal Abnormalities
  - Klinefelter's syndrome
  - Sex reversal
  - Familial true hermaphroditism
  - Streak gonads—XY karyotype
  - Testicular agenesis
  - Noonan's syndrome
  - Defective androgen synthesis
    - 20α-hydroxylase deficiency
    - 17,20-desmolase deficiency
    - 3β-hydroxysteroid dehydrogenase deficiency
    - 17-hydroxylase deficiency
    - 17-ketosteroid reductase deficiency
    - 5α-reductase deficiency
  - Adult seminiferous tubule failure and idiopathic oligospermia
  - Sertoli cell only syndrome
  - Acquired testicular disorders: orchitis, surgical castration, etc.
  - Myotonia dystrophica
- III. Defects in Androgen Action (Pseudohermaphroditism)
  - Complete androgen insensitivity, also called testicular feminization
  - Incomplete androgen sensitivity
    - Type I (after Wilson)
      - Rosewater's syndrome
      - Reifenstein's syndrome
      - Gilbert-Dreyfus syndrome
      - Lub's syndrome
    - Type II (after Wilson)
      - Also called pseudovaginal perineoscrotal hypospadias or 5α-reductase deficiency
- IV. Miscellaneous
  - Persistent müllerian duct syndrome
  - Cystic fibrosis

Isolated LH or FSH Deficiency, or Both

LH-FSH deficiency. This is a relatively common disorder and, as discussed, is frequently associated with hyposmia. Kallman's syndrome is described later, but has a variable presentation, and often only hypogonadism and hyposmia are noted; thus, separation of isolated LH-FSH deficiency from what is called Kallman's syndrome is not clear-cut and may be in part artifactual.

Isolated FSH deficiency. Rabin and associates[116] described a woman with primary amenorrhea, high LH concentrations in blood and undetectable FSH concentrations. Such findings (low FSH and high LH) are also observed in women with polycystic ovaries and testicular feminization syndrome. To our knowledge, a description of men with isolated FSH deficiency has not yet been published, but obviously such cases can exist theoretically. Since the absence of FSH in immature animals results in severely impaired LH action on Leydig cell function,[80,81] patients with congenital deficiency of FSH might be expected to have both decreased androgenization and decreased or absent spermatogenesis.

Isolated LH deficiency. Faiman and co-workers in 1968[117] described a well-evaluated patient with the so-called "fertile-eunuch" syndrome. This syndrome was originally described in 1950 by Pasqualini and Bur,[118] and they believed it was caused by an isolated deficiency of luteinizing hormone based upon (1) the absence of Leydig cells in presence of spermatogenesis on testicular biopsy and (2) the improvement in androgen function after treatment with human chorionic gonadotropin. In 1953, McCullagh and co-workers[119] described five patients and noted (using bioassays) normal urinary FSH excretion in all patients and low LH excretion in three of the five patients. Faiman and associates[117] evaluated a 20-year-old man with the clinical findings of eunuchoidism, with spermatogenesis present on testicular biopsy and an ejaculate analysis showing a volume of 1 ml and sperm count of 33,000,000 with no mortality. LH concentrations in serum and urine were repeatedly undetectable (below the sensitivity of the assay), while FSH concentrations were normal in both urine and serum. Treatment with clomiphene resulted in increased FSH concentrations, but LH remained undetectable. The patient received a course of human chorionic gonadotropin (HCG) episodically for several months and depotestosterone injec-

tions for several years; surprisingly, sperm count and ejaculate volume remained within normal limits 1½ years after the patient discontinued testosterone treatment. This is a relatively rare syndrome and to our knowledge additional patients of this type have not been studied.

Kallman's syndrome.[120,121] This syndrome typically consists of hypogonadism caused by LH-FSH deficiency, hyposmia or anosmia, often mental retardation, syndactyly, short fourth metacarpals, color blindness and nerve deafness. The syndrome is occasionally familial. A large number of patients are described in the psychiatric literature, before current laboratory testing procedures, and family members with hyposmia or anosmia without hypogonadism have been described. It is likely, therefore, that Kallman's syndrome is part of a spectrum of disorders all linked by hyposmia and hypogonadism. Generally, in such patients administration of clomiphene is not effective[121] and commonly there is an abnormal response on short-term LRH administration.[32]

Prader-Willi syndrome (HHHO syndrome). These patients typically are massively obese, mentally retarded, have hypogonadism and neonatal muscle hypotonia and often cryptorchidism. The syndrome was described by Prader, Labhart and Willi in 1956,[122] and in 1963 by Prader and Willi.[123] Zellweger and Schneider[124] have suggested the term HHHO syndrome (hypotonia, hypomentia, hypogonadism and obesity). Many of the described patients have been prepubertal, so that only recently[125,126] have more detailed studies of gonadal function been carried out in postpubertal boys. Figure 14 depicts a typical patient with this syndrome. Such patients usually die in the 20 to 35 age range with complications of massive obesity. They have uncontrollable hyperphagia and may have impaired temperature regulation both indicative of hypothalamic dysfunction. The hypogonadism also appears to be hypothalamic in origin. It is interesting to note that one of the patients reported in 1972 by Hamilton and associates[125] responded to clomiphene, and treatment for 40 days resulted in an increase of plasma testosterone and LH values to within normal limits, as well as development of normal spermatogenesis as shown by findings on testicular biopsy.

Lawrence-Moon-Biedl syndrome.[127,128] This is a heredofamilial syndrome, characterized by mental retardation, retinitis pigmentosa, hypogonadism and syndactyly or polydactyly. Detailed gonadal function studies, using current techniques, have apparently not been done.

Familial cerebellar ataxia.[129,130] This syndrome consists of familial cerebellar ataxia, nerve deafness and hypogonadotropic hypogonadism. Findings on x-ray studies of patients with familial cerebellar ataxia[130] and those with Lawrence-Moon-Biedl syndrome[127] show there to be short fourth metacarpals.

Laboratory Assessment of Patients in Category I

Since LH and FSH are secreted episodically, significant variations in serum concentration exist in an individual patient; therefore it is important, for accurate assessment, to measure these hormones in two to four independent blood samples. Blood testosterone should be quantified in at least one of these samples, and two independent determinations are preferable. If it is clear that any hypothalamic-pituitary cause of hypogonadism exists, it is probably *not* necessary to determine the karyotype of the patient, as normal XY is *expected*. It is important to note that the normal values for LH and FSH vary from laboratory to laboratory and must be carefully ascertained. In a carefully studied group of normal men, using the methodology in our laboratory, 244 samples were studied, average LH was 7.1 ± 2.6 (SD) milliinternational units (mIU) and two values were undetectable (<1.0), average FSH was 3.9 ± 2.0 (SD) and many samples were undetectable (<1.0). Using earlier methods in our laboratory five to seven years ago, values for LH and FSH were higher and normal was considered <25 mIU per ml for both FSH and LH. Tests for adequacy of pituitary secretion of hormones other than LH and FSH should also be done (for example, studies for insulin hypoglycemia, stimulation of growth hormone and adrenocorticotrophic hormone [ACTH]). Tests of gonadotropin releasing hormone (GnRH) stimulation of LH and FSH may be done, but it is important to note that the latter test does not reliably distinguish between hypothalamic disorders and pituitary disorders.[131] This is in contrast to the thyrotropin-releasing hormone (TRH) test, which does appear to separate these causes in thyroid-stimulating hormone (TSH) deficient subjects.

In addition to the above tests, testicular response to human chorionic gonadotropin may be

evaluated. Generally, a base line or control testosterone is measured. HCG (2,000-5,000 IU per day) is given for three to five days and repeat measure of testosterone level then obtained.

ERRORS IN TESTICULAR DEVELOPMENT

Klinefelter's Syndrome[69,91,132]

This syndrome accounts for the largest group of hypogonadal males with primary testicular abnormalities. Unfortunately, in our experience only the severely affected men are diagnosed by most physicians. Since the largest fraction of persons with this syndrome have a more subtle form of the disease, most are missed with the usual health screening techniques. This disorder then represents a broad spectrum ranging from men indistinguishable from normal except when examined by sensitive techniques, to blatantly hypogonadal men with severe hypoandrogenization, gynecomastia and tiny testes. There is little difficulty in recognizing the latter; the former often represent a difficult diagnostic challenge.

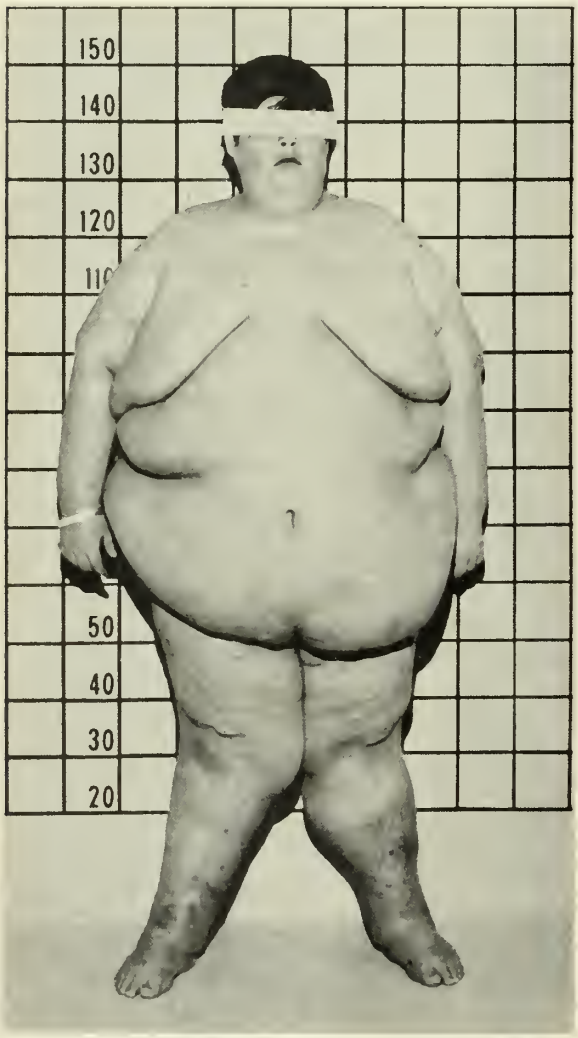


Figure 14.—Prader-Willi syndrome. Typical appearance of 15-year-old boy with this syndrome. This patient subsequently died from complications of massive obesity. (Reproduced through the courtesy of Robert Fiser, MD, Chairman, Department of Pediatrics, University of Arkansas School of Medicine, Little Rock)

A patient with so-called "classic" Klinefelter's syndrome is expected to have the XXY karyotype and consequently there would be abnormal findings on buccal smear—increased numbers of Barr bodies. The subtle varieties of this disorder are often associated with sex chromosomal mosaicism which can be associated with an intermediate or "normal" buccal smear Barr body count. While a buccal smear when "positive" in a hypogonadal man is indicative of a diagnosis of Klinefelter's or related syndromes, the absence of a positive smear should not dissuade a physician from the diagnosis. For this reason, we routinely carry out a karyotype determination.

We present two examples of Klinefelter's syndrome, representing more subtle forms of the disease.

CASE 1. A 28-year-old, unmarried male of Mexican-Indian ancestry was admitted to Harbor General Hospital for laceration repair. There was no complaint apart from this injury.

On physical examination no gynecomastia was noted. Phallus was normal and testes were bilaterally descended but measured only 1.5 by 0.5 by 0.5 cm. Beard, axillary and chest hair were within the broad limits of normal for Indian ancestry; pubic hair was modestly diminished. The patient's photograph is shown in Figure 15A. Height and span were equal; no abnormalities in sensation of smell existed.

Laboratory data included a karyotype of XXY, serum LH of 60 mIU per ml and a plasma testosterone value of 200 ng per 100 ml. Findings on testicular biopsy showed pronounced tubular atrophy, the rare preserved tubules containing only Sertoli cells.

CASE 2. A 76-year-old black man was admitted for control of diabetes mellitus. He reported having noted enlarged breasts at the age of 15; pubertal changes had not occurred until 18 to 21 years old. He was married twice. During his first marriage, three children were born to his wife. During his second marriage, of 23 years duration, his wife bore no children although she had had regular menses for several years and contracep-

tion was not practiced. His libido decreased during the last ten years, and he also noted decreasing axillary and pubic hair and testicular size. He believed that before this time, testicular size and body hair were well within normal limits (Figure 15B).

On physical examination the patient's height was found to be 69 inches and span 68 inches. Pronounced bilateral gynecomastia was noted. Beard was slightly diminished, axillary hair was present but limited to the apex. Pubic hair appeared moderately decreased. Testes measured 1 cm in length.

Laboratory data included serum LH concentrations of 44, 48 and 28 mIU per ml (normal = <1 to 15 mIU per ml) and a FSH value of 31 mIU per ml (normal = <1 to 15 mIU per ml). The plasma testosterone value was 90 ng per 100 ml (normal 400 to 1,200 ng per 100 ml). Karyotype 47 XXY/46 XY; findings on buccal smear showed no Barr bodies (normal findings on a buccal smear for a male).

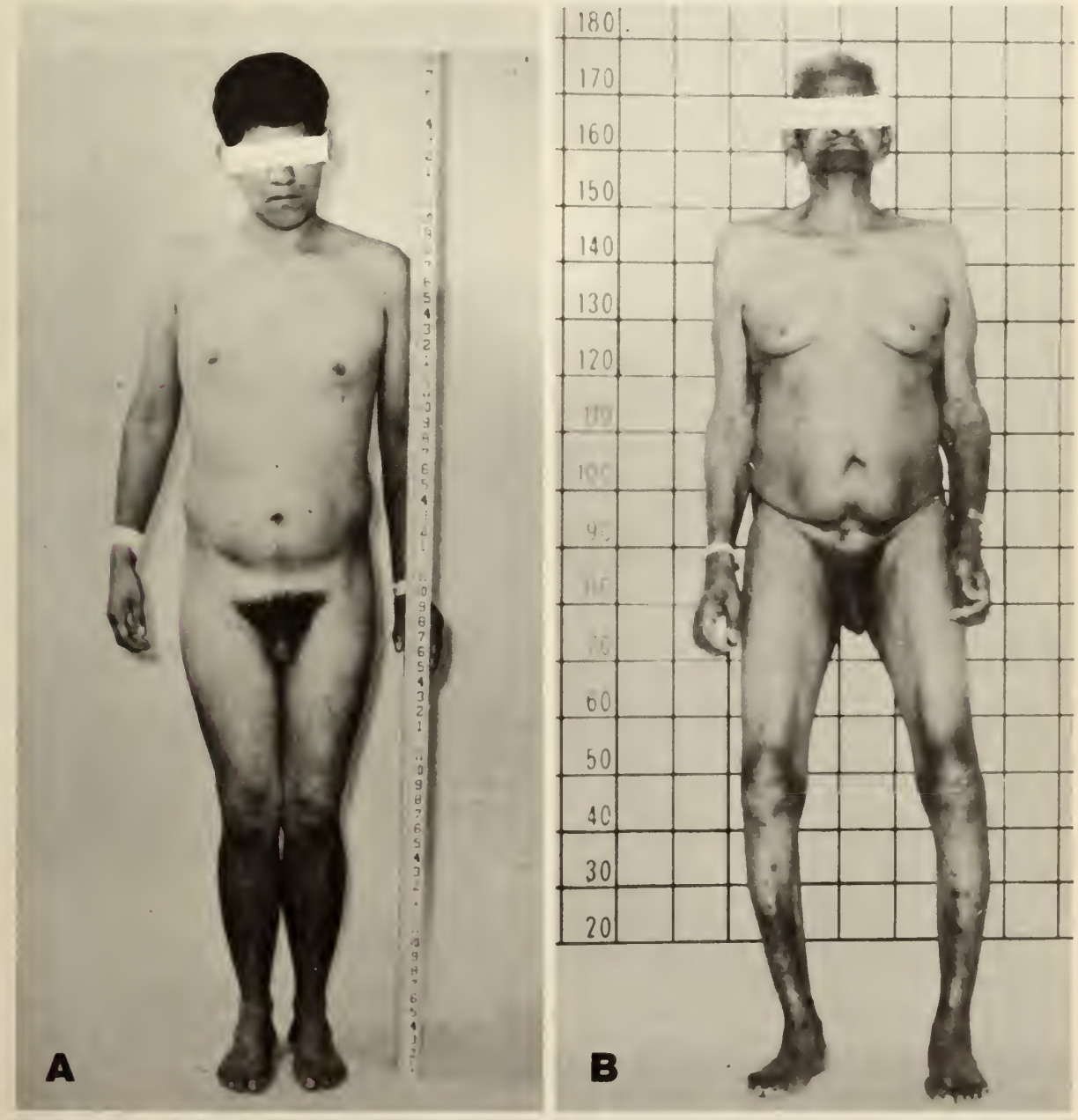


Figure 15.—**A,** a 28-year-old unmarried Mexican-Indian man with Klinefelter's syndrome; **B,** a 76-year-old black man with Klinefelter's syndrome.

This patient apparently had had a slightly late puberty and normal sexual function (as far as could be ascertained by history) during most of his adult life. Late in life there developed signs of decreased androgenization. We do not know for certain that the patient fathered the children born to his first wife.

Males with XX Sex Chromosomes

Clinically, these patients resemble patients with Klinefelter's syndrome. The disorder is rare, probably existing at only 1 to 10 percent of the frequency of Klinefelter's syndrome. Since the original descriptions of phenotypic human males with XX sex chromosomes were made in 1964,[133-136] approximately 50 patients have been described.

In 1972 De La Chapelle[134] reviewed the existing data on this syndrome. It was found to be not usually familial; with a single exception, cases have been sporadic. Kasdan and co-workers[137] recently described a pedigree strongly suggesting familial occurrence. Clinically, these patients present as phenotypic males, with testes and male psychosexual identification; no ovarian tissue or müllerian duct derivatives are present. The XX males appear to be shorter than XXY males; unlike Klinefelter's syndrome, the incidence of the XX syndrome is probably not increased in the mentally retarded. Gynecomastia occurred in 28 of 45 patients (62 percent), a similar incidence to that observed in Klinefelter's syndrome (40 percent).[132] Body hair is usually decreased and shaving is less frequent than normal. Pubic and axillary hair are also decreased. Penis and scrotum are often described as normal, though frequently the former is said to be small. Testes are small and when measured at surgical operation are usually 1 to 2 cm. Hypospadias is present in about 10 percent of patients, an incidence similar to that found in Klinefelter's syndrome.[132] Testicular histology is variable. It was reported as normal in two infants, two and eight months old.[138,139] In two children, ages one and two years, spermatogonia were absent, but histology was otherwise normal.[140,141] After the age of puberty the tissue more typically resembles that in Klinefelter's syndrome: absence of spermatogenesis, decreased tubule diameter, postpubertal hyalinization of tubules, peritubular fibrosis, and hyperplasia and polymorphism of Leydig cells. In some patients, a testis histology may resemble the "Sertoli cell only" syndrome in which tubules are normal or slightly reduced in size, but contain only Sertoli cells; Leydig cells are normal or slightly increased in number and do not show polymorphism.

This syndrome is of particular interest to endocrinologists and embryologists because if it truly is an XX syndrome, then testicular tissue has developed in the absence of a Y chromosome. Ferguson-Smith[141] has offered an explanation for this enigma by suggesting that an X-Y interchange may have occurred. Recently, Madan and Walker[142] described an XX patient, in whom the two X chromosomes were mismatched. They believe "Y" material may have been exchanged at meiosis, supporting Ferguson-Smith's hypothesis. Kasdan and associates[137] described two brothers and a paternal uncle with phenotypic maleness and XX karyotype. A 7½-year-old brother of the sibling patients, as well as their father, were normal phenotypic males with XY karyotype. In all the XX phenotypic male subjects, results of Barr body smears of buccal mucosa and skin, drumstick counts, repeated lymphocyte and skin karyotypes and quinacrine fluorescent studies of metaphase spreads, peripheral blood smears and buccal smears were all consistent with the observed sex-chromosome findings. The 31-year-old paternal uncle of the two affected siblings had a height of 166.4 cm, a lower segment height of 85 cm and a span of 171.5 cm. There was no gynecomastia and no hypospadias. Both testes were in the scrotum and of normal consistency, but measured 2.3 by 1.0 and 2.5 by 1.0 cm. He was azospermic. The FSH level was increased to over 1,250 μg per ml (normal = 60 to 390), the LH value was increased to 242 μg per ml (normal = 20 to 160) and the testosterone level was 541 μg per 100 ml (normal stated in paper as 732 to 1,896). In the two younger patients (ages 9½ and 7½), LH, FSH and testosterone values were appropriate for their ages.

True Hermaphroditism

The diagnosis of true hermaphroditism requires the presence of both ovarian and testicular tissue in the same person. According to Grumbach and Van Wyk,[91] gonadal stroma arranged in whorls, similar to that found in an ovary but lacking oöcytes, should not be considered as sufficient evidence to regard the gonad as an ovary. Similarly, testicular tissue is present in the

contralateral gonad; the presence of a few oöcytes in a streak gonad is not considered to be adequate evidence for the diagnosis of true hermaphroditism. The clinical features are variable. The external genitalia show varying degrees of sexual ambiguity. The spectrum of appearances includes that of fused scrotum and penile hypospadias to that of a female with a vaginal vault; often the external genitalia are ambiguous. Most patients are raised as males. The hypospadias present in most patients varies from that of a penile urethra with complete fusion of labioscrotal folds to a perineal urethra. Cryptorchidism is common, as is an inguinal hernia containing a gonad or uterus. In almost all patients a uterus is present. The genital ducts differentiate along the pattern predicted by the gonad; when a testis is present on one side, and an ovary on the other, the duct development is usually consistent with the type of gonad. Most patients have gynecomastia and many menstruate (Table 4).

Chromosomal analysis on a single peripheral tissue shows a variable pattern. Benirschke and co-workers[143] analyzed 119 reported patients and found the following distribution: 51 percent were 46 XX, 19 percent were 46 XY and 30 percent were chimeras and mosaics. However, these analyses are subject to great error and it appears that many more of the patients may be mosaics or chimeras. In the patient described by Benirschke and associates[143] culture of blood lymphocytes was done in 1967; cells contained 46 chromosomes and 3 metaphases were 46 XX. The patient was classified as such. In 1971, blood lymphocytes were again cultured and analyzed with the conclusion that 46 XY was present. Finally, these workers examined blood, skin, ovary, buccal smear and hair follicles using the Y fluorescent technique on touch preps as well as standard techniques and concluded the patient was a true chimera with 46 XX/46 XY admixture. In most patients such a detailed analysis has not been made, but it is well worthwhile.

TABLE 4.—*True Hermaphroditism*

- A variable spectrum; most patients have gynecomastia.
- External genitalia range from hypospadic male to nearly normal female.
- Cryptorchidism common, as is inguinal hernia containing gonad or uterus.
- Karyotype variable 46 XX, 46 XY or chimeras or mosaics (45 X/46 XY, 46 XX/46 XY, 46 XX/47 XXY, some without Y).
- Both testicular and ovarian tissues must be present.

Streak Gonads—XY Karyotype (Pure Gonadal Dysgenesis—XY Type)

These patients usually present as eunuchoid females with amenorrhea. None of the phenotypic abnormalities associated with Turner's syndrome are present. Height is *not* below normal and typically these patients are tall. Axillary and pubic hair growth occurs at a slightly older age than in normal females, but does occur, since adrenarche is apparently normal. Bone age is retarded (since gonadal steroids responsible for normal rate of bone maturation are deficient), and LH and FSH secretion are increased postpubertally. As indicated, the karyotype on all tissues that have been examined has been XY. While it has been postulated[144,145] that this syndrome may be associated with deletion of the long arm of an X chromosome (XXq-), chromosomal analysis in several tissues of five related females with this disorder showed normal XY karyotypes.[145]

Streak gonads, the absence of phenotypic abnormalities of Turner's syndrome in phenotypically eunuchoid females, also occurs in true XX persons, but is not discussed in further detail since it falls under the topic of female hypogonadism. Findings in several family studies of the streak gonad XY syndrome in phenotypic females have suggested that the syndrome is determined by an X-linked locus.

Testicular Agenesis (Vanishing Testis)

A person with this rare syndrome presents as a phenotypic male who is eunuchoid, has no testes palpable either inguinally or in the scrotum and has a normal XY karyotype. The testis may be absent only on one side and the other normal; in such patients hypogonadism is not present. Serum FSH and LH levels as elevated postpubertally and testosterone concentrations are low. Presumably, the testis has been present during embryogenesis to permit regression of the müllerian duct derivatives. Wolffian duct derivatives develop, but are not stimulated by androgen action as they would be in eugonadal men. This syndrome does not appear to be familial in nature. Abeyaratne and associates[146] have described 16 patients with this syndrome, 12 unilateral and 4 bilateral cases.

A vas deferens accompanied by testicular blood vessels, with or without a terminal knob of epididymis was shown to exist in almost all cases. Traced to its termination, which varied from iliac

fossa to scrotum, the vas ended blindly in 13 explorations and ended in a nodule of hypoplastic epididymus in 6 others. The fact that the testicular vessels reached the termination of the vas, suggests that the testis was originally present and attached to the mesonephric element and descended with it. The scarcity of epididymal elements suggests that some mesonephric tissue was lost along with the testes. Therefore, Abeyaratne and associates[146] suggested that the name "vanishing testis" is more appropriate than anorchia or agenesis.

Noonan's Syndrome (Male Turner's Syndrome; XX or XY Turner's Phenotype)

During studies on a large population of children with congenital heart disease, Noonan and Ehmke in 1963[147] described nine children (boys and girls) with pulmonary valve stenosis, short stature, hypertelorism, mild mental retardation, ptosis, undescended testes in boys and skeletal malformations. In these children there were many of the findings of patients with Turner's syndrome, but karyotypes were normal XY in boys and XX in girls. Since this publication, a large number of such children have been described. Nora and Sinha[148] described direct male to male transmission, and Bolton and co-workers[149] described a man and four of his sons affected with this syndrome. This and the fact that both males and females are affected, suggest an autosomal dominance inheritance pattern. Char and coauthors[150] described 45 patients with this syndrome. The phenotypic findings are quite variable and many patients may be difficult to identify. Short stature is extremely common in described patients and varies from pronounced short stature (below tenth percentile) to only low normal range. The father in Bolton's patients was 165 cm tall. Mental retardation is also very common, but not universally present. Again, the patients presented by Bolton were not at all retarded; the proband was a college chemistry teacher. Hypogonadism with undescended testes has been the usual finding, but some patients have descended testes and are fertile. Serum FSH and LH levels are elevated in postpubertal subjects, while typically the blood testosterone concentration is low to normal. Unexplainably, in Bolton's fertile patient there was high FSH and LH levels associated with abnormally high serum testosterone concentrations measured on several occasions. Other findings typical of Noonan's and Turner's syndromes are listed in Table 5. The skin findings (soft, hyperelastic skin) suggest that a widespread defect in connective tissue might be present; some patients have been erroneously diagnosed as having Ehlers-Danlos syndrome. Examined microscopically, blood vessels were found to be abnormal; disruption of the media by disposition of mucoid material and elastic tissue degeneration were present in all sections examined by Bolton and associates.[149]

TABLE 5.—*Noonan's Syndrome*

- Variable degrees of seminiferous tubule failure and decreased Leydig cell function associated with many phenotypic findings
- Karyotype normal XY (or XX in females)
- Associated phenotypic findings (variably present)
  - Short stature
  - Mental retardation
  - Cardiac lesions (frequently right-sided)
  - Hypertelorism
  - Webbed neck
  - Low posterior hairline
  - Chest deformity
  - Low set ears
  - Cubitus valgus
  - Hyperelastic skin
  - Undescended testes
  - Pes planus
  - Ptosis

Defective Androgen Synthesis

Five enzymatic defects have been described that result in impaired androgen synthesis (Table 6). Each of these defects (discussed below) is transmitted as an autosomal recessive trait. The degree of genitalia abnormality depends upon the completeness of enzyme deficiency and such patients range from nearly normal males with mild hypospadias to nearly normal females. The conversion of cholesterol to C21 and C19 steroids occurs by two pathways. These are summarized in Figure 4. In view of these two alternative pathways, more than one enzyme deficiency state can exist that affects the very early steps in conversion of cholesterol to androgens or to glucocorticoids.

Cholesterol desmolase complex deficiency (20α-hydroxylase deficiency) (lipoid adrenal hyperplasia). Prader and Gunter[151] and Prader and Anders[152] described a group of infants with severe adrenal insufficiency and large accumulations of lipids in the cells of the adrenal cortex and gonads. Affected males had female external genitalia and male genital ducts. Excretion of 17-keto-

steroid in urine was totally absent. Less severely ill patients have been described by Camacho and co-workers[153] and by Grumbach and Van Wyk.[91] In these patients there is absent or very low plasma cortisol levels, and absent urinary 17-ketosteroids, 17-hydroxycorticoids, pregnanediol, pregnanetriol or the 3β-hydroxy analogues of these steroids.

The patient of Camacho and associates[153] died with adrenal insufficiency when cortisol therapy was discontinued; that of Grumbach is alive at age 7 with treatment. Recently, Kirkland and co-workers[63] described a phenotypic female who survived two months of life without a crisis. Later in life, at age 8, urinary 17-hydrocorticoids and 17-ketosteroids were undetectable or near the "noise" level of the assay even after four days of ACTH therapy. Urinary cholesterol levels were increased, but a 20α-hydroxycholesterol was detected. Degenhart and associates[154] obtained adrenal tissue at autopsy from patients with this disorder and found deficient 20α-hydroxylation of cholesterol.

17,20-desmolase deficiency. Zachman and associates[155] reported two first cousins and their "aunt" with this syndrome. The cousins were 1.8 and 2.2 years of age when studied and had ambiguous external genitalia and inguinal gonads noted at birth. Their karyotypes were 46 XY, and findings on gonadal biopsy in each child showed immature testicular tissue. Urinary 17-oxysteroids and 17-hydroxysteroids were normal for age; pregnanediol and pregnanetriol were also normal. Pregnenetriol was over 10 mg per 24 hours, a highly elevated level. Testosterone concentration was unchanged after HCG stimulation; the same stimulation increased testosterone concentrations in a normal boy of the same age from undetectable to 8.3 μg per 24 hours. Incubated testicular tissue converted dehydroepiandrosterone (DHA) and androstenedione to testosterone freely, but could not convert progesterone or pregnenolone to testosterone.

The "aunt" was not evaluated in the same detail, but had an XY karyotype.

3β-hydroxysteroid dehydrogenase (3β-HSD) deficiency. The Δ^5 steroids must undergo dehydrogenation of the 3β-hydroxy group to permit shifting the Δ^5 double bond to the Δ^4 position. All of the gonadal and adrenal steroids having biological importance metabolically pass through this synthetic step. Bongiovanni and co-authors[156] described six such patients with this defect (three males and three females). Kenney and associates[157] described four patients (two males and two females).

Clinically these patients are found to have both cortisol and aldosterone deficiency. Genetic males with this syndrome usually present with ambiguous genitalia (severe hypospadias, bifid scrotum) due to their inability to synthesize normal amounts of fetal testicular androgens. DHA secretion is increased from adrenal sources; increased secretion of the weak androgen explains the occurrence of androgenized or ambiguous genitalia in genetic females with this disorder. Most of these patients are salt losers, although one of Bongiovanni's[158] original patients was described by Kenny and co-workers[157] to have refused cortisone treatment and at age 16 had not experienced any difficulty. In some of these patients there indeed has been shown to be normal cortisol production rates at the expense of increased adrenal stimulation. When studies are carried out in such patients in infancy, DHA excretion exceeds androsterone and etiocholanolone; when they are done later in life, the latter two may exceed DHA. Kenny and co-workers[157] discuss the evidence suggesting that 3β-HSD activities for various Δ^5 3β-hydroxysteroids do not appear simultaneously during fetal life. Activities of 3β-HSD for 17α-hydroxypregnenolone and 17-α-21-dihydroxypregnenolone appear earlier than do activities for pregnenolone and DHA, thus changing 3β-HSD activities—differing activities for different substrates—and substrate inhibition of the 3β-HSD activities helps to explain the changing excretion patterns and the preponderance of C-21 hydroxypregnenolone and pregnenetriol over the 19 carbon steroid DHA. Frequently, interpretation of plasma and urinary steroid patterns is complex and difficult to predict from the suspected enzyme deficiency. Significantly, for clinicians, these may result in erroneous interpretation of the enzyme defect present in a particular patient. Bongiovanni[156,158] found that pregnanetriol excretion was increased at times in patients with 3β-HSD deficiency; therefore measurement of this steroid alone should not be the sole criterion for differentiating 21-hydroxylase deficiency from 3β-HSD deficiency.

17-hydroxylase deficiency. Progesterone or pregnenolone must undergo 17-hydroxylation to permit formation of cortisol, estrogens or andro-

gens. Aldosterone synthesis does not require this step and, therefore, patients with 17-hydroxylase deficiency do not manifest mineralocorticoid deficiency. In 1966 Biglieri and co-workers[159] and in 1967 Goldsmith and co-workers[160] described females with this syndrome. Several additional females with this syndrome have been described since.

Subsequently, four male patients have been described.[161-163] Typically, these patients have ambiguous genitalia, hypertension, hypokalemia and XY karyotype. The patient of New[164] had pronounced gynecomastia, no secondary sex characteristic development, hypospadias, hypoplasia of the scrotum and an empty left scrotum.

As shown in Table 6, cortisol secretion in these patients is below normal. Plasma levels of ACTH, desoxycorticosterone (DOC) and corticosterone are increased. Since DOC secretion is increased, salt retention occurs and plasma renin and aldosterone concentrations are below normal. Furthermore, since testosterone and estrogen secretion are below normal, LH and FSH secretion is expected to be notably increased after puberty. FSH secretion would be expected to be moderately increased before puberty.

17-ketosteroid reductase deficiency. In 1971 and 1972 Saez and associates[165,166] first described a patient with this syndrome. This patient was considered to be a normal female until the time of puberty when normal breast development occurred, but simultaneously abundant body hair developed with male facial distribution, and the clitoris enlarged. Examination revealed a somewhat masculine body habitus and a normal blood pressure, and facial cheek hair and moustache. Pubic hair was "feminine" in distribution and axillary hair was normal. The clitoris measured 5.5 cm in length and 6 cm in circumference. The urethral orifice was posterior to the base of the clitoris and separate; the vaginal opening was narrow and about 5 cm deep. No uterus or cervix was present. A mass was palpable in each inguinal canal. Karyotype was 46 XY, gonadotropin excretion was increased. Detailed studies of steroid synthesis and secretion showed the changes described in Table 6.

In 1973, Goebelsmann and co-workers[167] described a second patient who was 46 years of age at the time of study. She was seen with a chief complaint of "hot flashes," sweating and hirsutism. Her history showed that she had never menstruated. Before puberty she was considered to be a normal female. At puberty breast development occurred, but in addition there were clitoral enlargement and excess body hair growth. Findings on examination included a male body habitus and a 46 XY karyotype. A blind vaginal pouch was present; uterus and cervix were absent.

In this patient there were increased blood levels of LH, normal blood levels of FSH and a pronounced increase in urinary 17-ketosteroid excretion. The concentration of testosterone in the blood was higher than found in normal females, but less than that in normal males. Serum androstenedione (A) concentrations were increased tenfold over normal male values and the A/T ratio was very high both in peripheral blood and spermatic vein blood. Kinetic studies showed that 91 percent of the peripheral testosterone was derived by peripheral conversion of androstenedione to testosterone. It also appears likely that some of these patients have been erroneously classified in other hypogonadal categories. For example, the 17-ketosteroid reductase deficiency may resemble the condition of a patient with incomplete testicular feminization, but having high ketosteroids.

5α-reductase deficiency. This enzyme is respon-

TABLE 6.—*Enzymatic Defects that Result in Impaired Androgen Synthesis*

Enzymatic Defects	*Cortisol*	*Androstenedione*	*Testosterone*	*Pregnenolone*	*Progesterone*	*17α OH Progesterone*
20α hydroxylase	↓	↓	↓	↓	↓	↓
3α hydroxysteroid dehydrogenase	↓	↓	↓	↓	↓	↓
17,20 desmolase	N	↓	↓	N or ↑	N or ↑	N or ↑
17 hydroxylase	↓	↓	↓	↑	↑	↓
17 ketosteroid reductase	N	↑	↓	N	N	N
5α-reductase	N	N	N	N	N	N

↓ = low levels
↑ = high levels
N = normal levels

sible for intracellular conversion of testosterone to dihydrotestosterone. For some tissues this is an obligate step in androgen action. Until very recently the disease syndromes produced by this enzyme deficiency were believed to be caused by a defect in androgen action. Thus, this disease is discussed in detail under defects in androgen action.

Adult Seminiferous Tubular Failures

The present concepts of control of testicular function have been presented earlier. When seminiferous tubular failure occurs in older men, it is seldom a significant clinical problem for practicing physicians because fertility is not usually desired by older men. Some studies have reported that testicular production of sperm declines in many older men, usually after 60 to 70 years of age. The cause or causes are not known. Amyloidosis is common in testicular tissue in older men and this may possibly be the cause in some. Paulsen[69] has indicated that in 15 to 25 percent of males with epidemic parotitis acute orchitis develops. Recovery or development of normal testicular function is expected if the process occurs before puberty; however, if the process occurs in adults, damage to tubular function is common. We have observed patients in whom the testicular failure was first diagnosed more than 20 years after the mumps orchitis; Paulsen[69] makes the same observations. Typically, the testes are soft and smaller than normal. While in most patients only sperm production is impaired, in a small percentage both Leydig cell and tubular failure is present.

Idiopathic oligospermia in young men is probably the most common category of hypogonadism and presents to physicians as the therapeutically difficult problem of male infertility. This disease is associated with normal androgenization, normal finding on physical examination in all aspects except occasionally slightly small testes, normal serum testosterone concentrations, normal serum LH levels and normal or slightly elevated serum FSH levels. The cause is unknown at present and treatment is difficult and usually ineffective. A great deal of study is desirable in this poorly understood area.

Sertoli Cell Only Syndrome

This is a rare syndrome in which Leydig cell function is completely normal, but sperm production is decreased. There are no abnormal physical findings except the findings of testes slightly below normal size in some patients—findings on biopsy include tubules devoid of mature sperm and tubules lined only with Sertoli cells. The patients present with infertility. Blood LH concentrations are normal; FSH concentrations are increased. Biopsy studies of these testes find that the tubules are devoid of germ cells and are reduced in size. Peritubular sclerosis and hyalinization are not present. Leydig cells are normal. The cause of this syndrome is uncertain. Abnormalities of chromosome complement are unusual; one of ten patients examined, for example, had XYY karyotype, the remaining nine patients had normal XY karyotype.[69,168-171] This syndrome may be classified as a subcategory of adult seminiferous tubular failure.

Acquired Testicular Defects

We have included this category for completeness. Obviously, surgical castration or testicular destruction by infection, interference with vascular supply and the like may impair function.

DEFECTS IN ANDROGEN ACTION

In this interesting and major category of male hypogonadal states, there does not appear to be any defect in the hypothalamic-pituitary-testicular axis. Androgens are made in amounts normal or above normal for eugonadal adult men, but because of various defects in the tissue action of these androgens, the men are not fully androgenized. There is a spectrum of abnormalities of this type depending upon the tissues affected and the severity of the end organ defect. Certain animal models exist and a brief discussion of those sets a background for discussing pathophysiology. Testicular feminization is known to be an inherited disorder in men, rats, mice and cattle. In these species, the affected male has external genitalia and breasts characteristic of phenotypic females, an absence of internal genitalia other than testes and resistance to androgen action. The abnormalities in phenotype are believed to be explainable by the absence of *effective androgen action;* as discussed in the first pages, differentiation of the male internal and external genitalia is mediated by androgens secreted by fetal testes. At a cellular level, androgen action requires (1) binding to cytosol binding proteins, (2) structural modification of the cytosol receptor androgen complex, (3) transfer of the cytosol-receptor androgen complex to the nucleus, (4)

binding of the complex to nuclear chromatin and (5) the series of DNA, messenger RNA mediated steps that ultimately modify protein synthesis and cellular function. (We combine these later steps for this discussion since they are apparently not faulty in these syndromes, and therefore do not need to be discussed in detail.) Since androgens affect most body tissues, such cytosol binding proteins are predictably found in many tissues.

In 1972 Bullock and Bardin[168] reported in the mouse and rat models of testicular feminization that kidney and preputial gland cytosol receptors were absent; whereas, in normal rats and mice, such receptors were easily shown to exist. They postulated that the disease in these animals was caused by absence of these receptors.

However, Goldstein and Wilson[172] showed that the picture was more complex. In the mouse model, they showed there to be four abnormalities:

- Serum testosterone was low (in contrast to the human disease counterpart). Testosterone formation in testicular slices from 6- to 8-week-old affected males was diminished. However, testosterone synthesis was identical in testes from *newborn* affected and from normal males (suggesting this defect in synthesis was acquired).
- Virilization of female litter-mates of the affected animals did not occur when the mother was treated with large doses of exogenous testosterone during pregnancy.
- Metabolism of testosterone to dihydrotestosterone was normal in fetal anlage of sex accessories (urogenital sinus and genital tubercle); whereas, this metabolism was notably diminished in the male accessory organs of the adult testicular feminization animal.
- Deficient binding of testosterone to the nuclei of the submaxillary gland (a known androgen sensitive tissue) was present.

These findings suggest that two prominent features of this syndrome in mice (the decreased testosterone synthesis and deficient conversion of T to DHT) are secondary defects caused by some different primary defect. In addition, the findings of these workers that T is metabolized to DHT normally in tissues from newborn animals with testicular feminization shows that this capacity for metabolism is an inherent ability of the tissue and not one derived from androgen stimulation per se (since the animals with testicular feminization are unresponsive to androgens). Goldstein and Wilson[172] also showed that in normal males, DHT formation is lower in the wolffian ducts than in the normal adults. This suggests that tissues derived from the wolffian ducts (seminal vesicles and epididymis) acquired or notably increased their ability to metabolize T to DHT. This is in contrast to the previously discussed nonwolffian duct derived tissues.

Therefore, although showing there to be a variety of defects in adults, Goldstein's and Wilson's data are compatible with a defect in androgen action at events after the conversion of T to DHT. It is now generally agreed that some cytosol receptors (for example, prostate) bind both T and DHT; T is bound less avidly than DHT. It is possible, therefore, that the latter step suggested by Goldstein and Wilson[172] is in fact the absence of cytosol receptors suggested by Bullock and Bardin.[168] It remains possible that the lack of receptors is also one of the acquired defects of this disease. However, it appears most likely that the defect is either receptor absence or one step further—that is, transport and binding of the androgen receptor complex to the nuclear chromotin.

Testicular Feminization Syndrome

Complete form. This syndrome is an X-linked recessive trait or male limited autosomal dominant[91] probably resulting from a biochemical defect in androgen action. Consequently XY males show no response to androgens either during embryogenesis or throughout life. Studies in tissues from men with this disease showed low rates of formation of DHT[173,174] and it was postulated that this might be the cause of the disease. However, the studies previously described in animals suggest this is an acquired defect. In addition, it was shown[173] that tissues from patients with 17-hydroxylase deficiency convert T to DHT at even lower rates than do tissues from patients with testicular feminization. Since 17-hydroxylase deficiency has no direct involvement in T to DHT conversion, this low conversion rate is presumably an acquired defect in these patients.

The *complete form* of the disease is characterized by a phenotypically normal female appearance.[175] Patients consider themselves psychologically to be female and usually many have normal heterosexual attitudes and relations. They are amenorrheic and infertile; amenorrhea usually is the complaint that brings them to the physician. These patients undergo feminization at puberty with excellent estrogen effects on skin, body fat

distribution, breast development, voice and so forth. Typically, axillary or pubic hair does not develop because those events are androgen stimulated. Findings on physical examination include (1) a phenotypically normal female except for the absence of body hair, (2) often the presence of palpable gonads (testes) in the inguinal canals, (3) a blind often short vaginal pouch and (4) no cervix visible and uterus or ovaries not palpable. There is often the history that the inguinal masses (gonads) are tender or sensitive to contact. On laboratory evaluation there are an XY karyotype and blood testosterone concentrations that are normal or frequently above that for eugonadal men. LH concentrations are generally high, but not in the castrate range; FSH concentrations are normal. After gonadectomy both LH and FSH levels increase to castrate levels.

TABLE 7.—*Testicular Feminization*

- Characterized by phenotypically normal female appearance with absence or deficiency in body hair.
- Estrogen effects are as in normal females.
- No cervix; inguinal or intraabdominal testes are present.
- Laboratory findings show XY karyotype, high serum levels of luteinizing hormone, normal serum levels of follicle-stimulating hormone and blood testosterone concentrations similar to or higher than in eugonadal males.

TABLE 8.—*Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH), Testosterone and Estradiol Concentrations in Blood*

	Normals	*Testicular Feminization*
Testosterone ng/ml	5.6±0.4*	10.6±1.3
LH mIU/ml	13.1±1.1	34.8±8.4
FSH mIU/ml	9.1±0.5	6.5±2.4
Estradiol μg/day	45*	122*

(Prepared from data published by Judd, et al.[176])

*Normal testosterone, estrone and estradiol values from Wilson, et al;[178] estradiol in normals is the average of four men studied; testicular feminization value is from a single patient only.

TABLE 9.—*Concentrations of Testosterone, Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH) and Estradiol (E_2) in Blood in Male Pseudohermaphroditism*

	Normal Men	*Type I*		*Type II†*
Testosterone ng/ml	6.1±0.5	9.2±0.54(9)‡		6.9
LH* ng/ml	50±3	111±9.2(9)	46.5	5.4
FSH ng/ml	223±13	150±32(9)	254	9.2
E_2 pg/ml	26.1±2.3	34(2)		22

*ng/ml LER 907 reference preparation; the same relative differences between normal men and Type I pseudohermaphroditism exist when samples are quantified in mIU/ml. Thus, in Type I patients there are only slightly increased blood LH and FSH levels.
†Data from Wilson, et al[178] and Walsh, et al.[185] Type II data from one patient; for LH and FSH five samples from same subject were averaged.
‡Numbers in parentheses indicate numbers of subjects studied.

Estradiol and estrone concentrations are above the range found in normal men, explaining the excellent effects that estrogen has in these patients. Tables 7 and 8 summarize some aspects of the testicular feminization syndrome.

Treatment of these patients consists only of appropriately timed gonadectomy, followed by estrogen replacement. Since they feminize normally at puberty due to estrogen action unopposed by any androgen actions, it is generally suggested that gonads remain until after puberty. Because the incidence of malignancy in the ectopic testes is increased to a pronounced degree, usually presenting in the 30's in these patients[175,177] gonadectomy is recommended between the ages of 18 and 25.

Male Pseudohermaphroditism

Wilson and co-authors[178] have divided this category into two types based on genetic considerations. Type I is inherited as an X-linked recessive trait; Type II is inherited as an autosomal recessive trait.

Type I. This category consists of a spectrum ranging from patients with an almost complete absence of virilization to moderately hypogonadal males. Lubs and associates[179] described a family who are on the feminine end of this spectrum. Four of five affected members were raised as females, but contrasted to patients with testicular feminization in that partial wolffian development, partial labialscrotal fusion occurred and axillary and pubic hair and a masculine body habitus developed. Gilbert-Dreyfus and associates[180] described a family in the middle of the spectrum. In affected members, body habitus was masculine, phallus was small, hypospadias was present and some wolffian duct development and gynecomastia occurred. The next step in the spectrum may be represented by Reifenstein's syndrome which is characterized by generally masculine body habitus and perineoscrotal hypospadias. Occasionally a bifid scrotum is present. At the usual age of puberty, gynecomastia develops. Rosewater and co-workers[181] described a mild form of incomplete male pseudohermaphroditism. The males had gynecomastia and sterility without other abnormalities of external or internal genitalia. Wilson and associates[178] described a large family with Type I male pseudohermaphroditism in which the phenotype varied in affected members from a minimal defect in virilization (micro-

phallus and bifid scrotum) to a more severe abnormality (perineoscrotal-hypospadias) to the most severe form (perineoscrotal hypospadias, absent vas deferens and vaginal orifice). A similar family was reported by Walter and associates.[182]

The fact that within a single pedigree, manifestations of the disease range over the entire spectrum from feminine-like presentation to nearly normal males suggests strongly that Wilson's classification is correct. Furthermore, since female internal genitalia are absent in this spectrum, müllerian regression must be normal. The basic defect must, therefore, lie in androgen synthesis or action. Findings in the studies of Wilson and co-workers[178] showed serum testosterone and LH concentrations tended to be above normal. Table 9 summarizes these data. We recently have investigated a similar family in which affected members have bifid scrotum hypospadias and gynecomastia. These patients have had very high serum testosterone and estradiol levels, elevated serum LH and normal FSH concentrations. Figure 16 schematically depicts sources and amounts of estrone and estradiol production in patients with testicular feminization and Type I male pseudohermaphroditism.

Type II (pseudovaginal perineoscrotal hypospadias). This defect was originally described as pseudovaginal perineoscrotal hypospadias by Opitz and co-workers.[183] Their descriptions and the subsequent studies by Walsh and associates[185] show that it consists of a constellation of 46 XY male pseudohermaphroditism transmitted as an autosomal recessive, the absence of female internal genitalia, the failure of breast development at puberty and the presence of adult male blood levels of testosterone, estradiol, LH and FSH. These patients have partial virilization at the time of puberty, cliteromegaly and underdevelopment of the vagina.

Walsh and co-workers[185] described a well studied sibship with two members having the Type II defect. Their index patient was thought

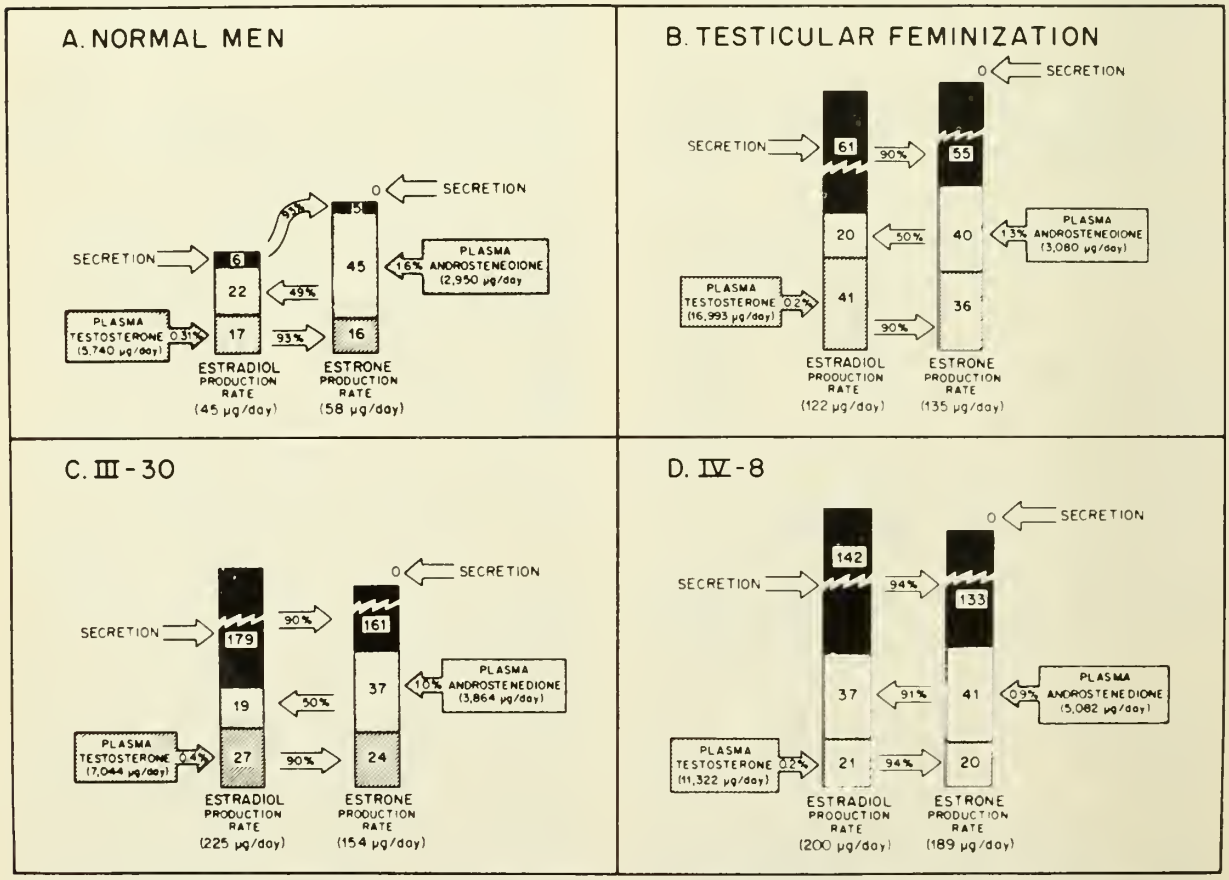


Figure 16.—Schematic presentation of sources of estradiol and estrone in **A**, normal men, **B**, men with testicular feminization and (**C** and **D**) two patients with incomplete male pseudohermaphroditism, Type 1. (Reproduced by permission from Wilson JD, et al[178])

to be a normal female until age 13 when the family noted failure of breast development, failure of menarche and a deepening voice. On examination, she had a masculine habitus, low voice, no breast tissue, bilateral inguinal masses, a phallus of 5 by 1.5 cm and a 5 cm blind vaginal pouch. Karyotype was 46 XY. Plasma LH, FSH, testosterone, estradiol and estrone were all within the range of normal men (Table 9). At exploratory laparotomy, no uterus or other female sex accessories were found. The inguinal masses were testes (4.0 by 2.5 by 1.5 cm), which were removed. The vas deferentia were dissected and contrast media injected; then on x-ray studies, bilateral ampullae of the vas deferentia, normal seminal vesicles and normal ejaculatory ducts emptying into the vagina were seen.

The second patient was noted to have cliteromegaly at birth. At 2½ months of age, a negative buccal smear was obtained and gonads were palpated in the labial folds. No evidence of a vaginal orifice was present. At laparotomy, no female sex accessories were noted, and both gonads (testes) were removed. She was raised as a female and did not note by age 11 any pubertal growth spurt, breast enlargement, masculine habitus or pubic hair development. Karyotype was determined to be 46 XY. Imperato-McGinley and co-workers[186] reported investigation of 12 families containing 22 pseudohermaphroditic subjects from a village in the Dominican Republic. Physical findings were identical to those typified by the patients above. In addition, these workers showed that during testosterone infusion only 1 percent was converted to DHT (normal 4 to 7 percent).

The defective virilization in this disorder is limited to the urogenital sinus and anlage of the external genitalia. As previously discussed, the process of virilization of the male fetus is very different in the urogenital sinus and tubercle as compared with the wolffian duct. Testosterone per se appears to be the intracellular mediator for wolffian duct differentiation into epididymus, vas deferens and seminal vesicles. Intracellular conversion of T to DHT does not occur until differentiation is far advanced. In contrast, in the urogenital sinus and tubercle the ability to convert T to DHT is present before male sexual differentiation. Thus, it is believed that DHT is the responsible hormone. It is postulated by Wilson and associates[178] and Walsh and co-workers[185] that Type II pseudohermaphroditism is caused by failure of conversion of T to DHT. The result is failure of differentiation of specific tissues. The predicted result of such a theoretical defect would be those abnormalities observed in Type II pseudohermaphroditism. The findings of decreased conversion of T to DHT by Imperato-McGinley and co-workers adds further support to this hypothesis. These workers attributed their patients' disease to 5α-reductase deficiency.

MISCELLANEOUS DISORDERS

Persistent Müllerian Duct Syndrome[187,188]

This syndrome is caused by a defect in müllerian duct regression in XY males. Patients usually presented as phenotypic males with inguinal hernias, cryptorchidism and otherwise normal external genitalia. When hernia repair is carried out, uterus and fallopian tubes are found in the inguinal canal. Wolffian duct derivatives are normal male in type although in some, the vas deferens courses through the uterus. Several families have been reported with several affected males suggesting that inheritance is via an autosomal recessive trait. The cause appears to be deficiency in elaboration of, or elaboration of an abnormal, müllerian regression factor.

Cystic Fibrosis[189]

Males with cystic fibrosis are infertile because of failure of development of the vas deferens. In some patients the seminal vesicles are absent and the epididymus immature. The prostate and external genitalia develop normally. These would appear to be defects in differentiation of wolffian duct derivatives, and it is uncertain whether this is an associated primary defect caused directly by the cystic fibrosis gene or an embryonic effect related secondarily to the prime gene action.

LABORATORY EVALUATION OF PATIENTS IN HYPOGONADAL CATEGORIES II, III, IV

Although the total numbers of diagnostic categories may seem overwhelming, diagnostic principles are not complex. The data or information

TABLE 10.—*Laboratory Data for Patients in Hypogonadal Categories II, III and IV*

Genetic Sex
Presence or absence of gonads
Functional state of gonads
Blood testosterone concentrations
Blood luteinizing hormone and follicle-stimulating hormone concentrations

shown in Table 10 must be available. It is always necessary to specifically determine genetic sex in patients in Categories II, III and IV of Table 3. Karyotype determinations may be difficult to positively interpret and occasionally more than one tissue must be studied. The Y fluorescence technique is very useful. Whether gonads are present or not may be determined in an adult with good (but not perfect) reliability by several determinations of blood LH and FSH concentrations. With absent gonads these should consistently be in the castrate range with FSH:LH ratios of >1, stated in terms of the International Reference Preparation for LH and FSH (IRP HMG No. 2). Tests of testicular response to HCG may be of additional help in deciding if gonads are present. If gonads are present in any location, the likelihood of their becoming malignant must be determined. Blood testosterone determinations should be made at least twice, and LH and FSH quantified on a minimum of three independent samples. Usually with these data and the history and physical examination findings, the diagnostic possibilities may be narrowed to from one to a few possibilities. Additionally specific laboratory tests, particularly if enzyme deficiencies are suspected, may be required in some patients. These tests would include blood or urine steroid determinations to delineate the enzyme block, and occasionally ACTH stimulation to magnify the steroid synthetic defect.

To adequately treat any of these patients, a firm decision of appropriate sex assignment must be made. This may not be identical to genetic sex. Reference to Table 3 illustrates some instances where assigning the male sex to a patient with XY karyotype would be unwise and unhelpful. Consideration of all of these diagnostic possibilities in infants with ambiguous genitalia is essential also if sex assignment is going to be wisely made early in life.

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Refer to: Lung abscess—Medical Staff Conference, University of California, San Francisco. West J Med 124:476-482, Jun 1976

Lung Abscess

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *We have recently encountered a patient on our service in whom there is a slowly resolving lung abscess. In fact the cavitary lesions spread despite vigorous therapy with penicillin G. It was only after therapy was shifted to clindamycin that a clinical and radiologic response was obtained. We have asked Dr. John F. Murray, Chief of the Chest Service at the San Francisco General Hospital, to discuss this patient and the general problem of lung abscess. A case summary of our current patient will be presented as a background for this discussion.*

Case Summary†

A 30-year-old man was recently admitted to the Moffitt Hospital Medical Service complaining of cough and fever of four months' duration.

Five months previously, during an episode of mild gastroenteritis, findings on a roentgenogram of the chest were reported as normal. Three weeks later, he was admitted to San Francisco General Hospital because of disorientation and catatonic behavior; subsequently, he was transferred to Napa Psychiatric Hospital where an infiltrate of the left upper lobe was noted on a roentgenogram of the chest. After five days of cephalexin (Keflex®) therapy, it remained the same size and showed some evidence of cavitation (Figure 1); the patient was transferred back to San Francisco General Hospital. Intradermal skin tests for coccidioidomycosis and histoplasmosis were negative, but the tuberculin skin test was positive. Sputum smears were negative for acid-fast bacilli, and while cultures were pending, isoniazid, 300 mg per day, and rifampin, 600 mg per day, were administered. Four weeks later, low-grade fever and cough productive of fetid sputum were still present, and there had been no improvement in the roentgenographic appearance of the left upper lobe cavity. Cultures of sputum for acid-fast bacilli were negative. Bronchoscopy was carried out and findings included inflammation and narrowing of the apical-posterior segmental bronchus of the left upper lobe, but no diagnostic lesions were identified. Cytologic examination showed no abnormalities and acid-fast bacilli and fungal cultures were again negative. Two weeks later, on a roentgenogram of the chest, enlargement of the cavity to a diameter of 6.5 cm was noted and hilar adenopathy was present (Figure 2). A Gram stain of sputum showed primarily Gram-negative organisms, and cultures of transtracheal aspirates yielded mixed flora, including Bacteroides species.

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†John Meyer, fourth year medical student.

Figure 1.—Roentgenogram of chest obtained in October 1975 showing a distinct cavity in the left upper lobe with an air-fluid level and left hilar adenopathy.

Figure 2.—Roentgenogram of chest obtained in December 1975 showing progression in the size of the cavity and fluid and an increased prominence of hilar adenopathy.

Serum titers for histoplasmosis and coccidioidomycosis were within normal limits.

A diagnosis of anaerobic abscesses was made and penicillin therapy, 12 million units per day given intravenously, was instituted. Isoniazid therapy was continued, but rifampin was discontinued. After nine days of penicillin therapy, no improvement in cavity size was apparent; the patient left the hospital against medical advice but continued to take isoniazid.

Two and a half weeks later, the patient presented to the University of California Hospital complaining of a cough productive of approximately one cup of grayish fetid sputum per day, persistent fever and anorexia. The patient said that there had been no history of seizure disorder, or use of intravenous or sedative drugs or alcohol.

On physical examination, the patient was thin, coughing and appeared chronically ill. Temperature was 100°F (37.8°C). The teeth were in moderately good repair. A few small nontender nodes were palpable in the anterior cervical chain. Examination of the chest showed no abnormalities. On cardiac examination, a soft systolic ejection murmur was noted. There was 4+ clubbing of the nails. The patient was anemic, and serum and total iron-binding capacity were both below the lower limits of normal. Leukocyte

Figure 3.—Roentgenogram of chest obtained in early February 1976 showing the appearance of a new cavity in the upper portion of the left lower lobe.

count was within the normal range, but the sedimentation rate was elevated. Treatment with 2.4 million units of penicillin per day given intravenously was instituted and then the dosage was increased to 10 million units per day. After 13 days of penicillin therapy, the patient was still febrile, but sputum production was diminished. On a roentgenogram of the chest a new cavity in the left lower lobe was seen (Figure 3). Administration of penicillin was discontinued, and treatment with clindamycin hydrochloric acid, 2.4 grams per day given intravenously, was begun. After 72 hours, the patient became afebrile and was much improved clinically. Seven days later, findings on a chest roentgenogram showed that the cavity in the left upper lobe and surrounding infiltration were beginning to resolve (Figure 4). Oral administration of clindamycin, 2.4 grams per day, and isoniazid were prescribed and the patient was discharged 4½ months after onset of the illness. The patient is being followed in the Chest Clinic.

Dr. Murray:* Lung abscess can be defined as a necrotic lesion in the lung parenchyma that contains pus. This broad definition means that a number of processes must be considered when evaluating a patient with a suspected abscess.

*John F. Murray, MD, Chief of the Chest Service, San Francisco General Hospital; Professor of Medicine, University of California, San Francisco.

Figure 4.—Roentgenogram of chest obtained in late February 1976 showing collapse of the left upper lobe cavity wall.

Lung abscesses can be caused by necrotizing infections of the lung parenchyma, by secondary infection or bland necrosis of infarcted lung tissue or by cavitation in the necrotic center of malignant lesions. Perhaps the most important of these is necrotizing infections.

A variety of infectious agents can cause a lung abscess (Table 1). These are the pyogenic bacteria (including staphylococci, Klebsiella, and other Gram-negative organisms), a variety of anaerobic microorganisms and occasionally Nocardia. Mycobacteria obviously are an important cause of lung abscess, although we usually refer to the lesions produced by mycobacteria as cavities; in fact, they are caused by necrosis of lung tissue and often contain pus, so they certainly fall into our definition of an abscess. Mycobacterium tuberculosis and a variety of other so-called atypical mycobacteria are well known causes of lung abscess. Several fungi can cause lung abscess. In this country, particularly, coccidioidomycosis and histoplasmosis are not uncommon and, of course, are found in certain geographic locations. Elsewhere, parasites may be an important cause of lung abscess. In Korea, Northern China and other parts of the Orient, lung abscess from Paragonimiasis westermani (the lung fluke) is common. In South America and other parts of the tropical regions of the world, amebiasis is an important cause of lung abscess.

Cavities in the lung may also occur from devitalized tissue resulting from a variety of vascular lesions. Pulmonary infarction from an ordinarily bland pulmonary embolus, if large enough, can be associated with cavitation. Septic emboli, however, are much more likely to cause cavitation. Most such abscesses occur in drug addicts, and the causative organism is usually Staphylo-

TABLE 1.—*Types of Lung Abscess*

- Necrotizing Infections
  - Pyogenic bacteria (Staphylococcus, Klebsiella, anaerobes, Nocardia)
  - Mycobacteria
  - Fungi
  - Parasites
- Cavitary Infarction
  - Bland
  - Septic
  - Vasculitis
- Cavitary Malignancy
  - Primary
  - Metastatic
- Other
  - Infected cysts
  - Necrotic conglomerate lesions

coccus. Occasionally, anaerobes and more rarely Candida will produce multiple septic cavitary lung abscesses. Vasculitis is a somewhat unusual cause of infarction that may cavitate; however, this is a well-known complication of Wegener's granulomatosus and periarteritis of the lung. Finally, some malignancies may cavitate. A variety of primary bronchogenic carcinomas are known to cavitate, including virtually all cell types except perhaps the bronchoalveolar cell tumor. Metastatic lesions may also cavitate, although far less commonly than primary lung tumors. Preexisting bronchogenic cysts or sequestrations of the lung can become infected and necrotic, but this is rare. Finally, the conglomerate lesions associated with certain kinds of pneumoconiosis, particularly silicosis and coal miners pneumoconiosis, can aggregate and in the absence of secondary infection become necrotic. In the United States, necrotizing infections are the most common cause of lung abscesses, and the most common causative microorganisms are the anaerobes and mycobacteria.

This leads us to consideration of the pathogenesis of lung abscess and the mechanisms whereby various anaerobic microorganisms reach the lower respiratory tract and produce infection and of the major role of aspiration. I do not discount the importance of pyogenic lung abscesses caused by Staphylococcus and Klebsiella and will discuss these as key points in the differential diagnosis and the evaluation of patients for initial antimicrobial therapy.

Aspiration is, in fact, a common event. Dye placed within the stomachs of patients before they undergo surgical operation and receive a general anesthetic can be recovered in the airway in from 10 to 15 percent of the patients. Similarly, dye placed in the oropharynx of patients with tracheostomies (uncuffed) appears in aspirates from the tracheostomy tube in nearly 70 percent of the patients. Contrast material placed in the nasopharynx of sleeping patients can be seen in radiographs of the tracheobronchial tree obtained the following morning. These observations mean that aspiration probably occurs frequently and that it is largely unrecognized. It is, therefore, not usually associated with significant clinical sequelae. One must conclude that lung disease occurring in association with aspiration probably depends upon the frequency, the volume and the character of the material that is aspirated.

The frequency and the volume of the aspirate are influenced by the underlying clinical condition. One such condition is a reduced level of consciousness. This, in turn, is associated with an impairment of protective cough reflexes and a loss of the normal functions of glottic closure; therefore, the upper airway is not as well protected as it normally is. Another obvious underlying condition that promotes frequent aspiration and affects the volume of material aspirated is the presence of swallowing difficulties. Mechanical disruption of the lower esophageal sphincter particularly from the presence of a nasogastric tube may also contribute to aspiration. Accordingly, we can list the clinical conditions in which aspiration is likely to occur and hence favor the development of pyogenic lung abscess. These include alcoholism, seizure disorders, cerebrovascular accidents, drug addiction, general anesthesia, esophageal disease and feeding by gastric tube.

The character of the aspirate is important for two reasons: first, because it determines the bacterial load, or the quantity of microorganisms that may be aspirated into the lower respiratory tract, and second, because associated components of the aspirate may affect the potential of the microorganisms to produce infection in the lung. Gastric juice with a low pH promotes a chemical pneumonitis facilitating implantation of microorganisms. Food particles or debris impair normal clearance mechanisms and allow microorganisms to reside in the lower respiratory tract longer than normal. Judging from experience in the preantibiotic days, once aspiration has occurred, it appears to take from 8 to 14 days for infection with necrosis to occur. This is important because it obviously means that there is an insidious onset with a smoldering increase in the clinical manifestations of aspiration pneumonitis and pneumonia and its complications. Consequently, most large series report that patients are symptomatic for at least 12 days before admission to hospital, and often, as in the case presented today, cough, sputum production and manifestations of infection may be present for periods of several weeks, or even months. Fever, weight loss, leukocytosis, anemia and other evidence of prolonged systemic infection can be expected and are important features of so-called chronic lung abscess.

The state of oral hygiene is the other condition that is implicit in the notion that the bacterial load is an important determinant in the pathogenesis of lung abscess. Large numbers of bacteria exist normally in the mouth and oropharynx. Anaerobic microorganisms outnumber aerobic micro-

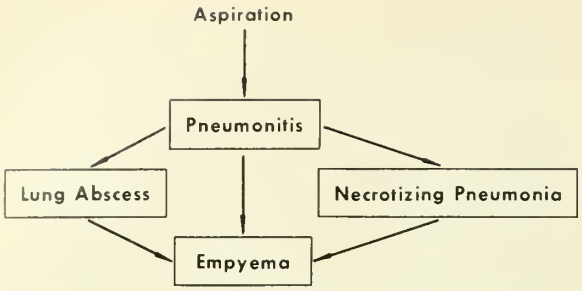

Figure 5.—Sequence of events after aspiration of infective material in anaerobic pulmonary infections. The initial process is pneumonitis that may progress to lung abscess or necrotizing pneumonia. If the infection involves the pleura, empyema will develop.

TABLE 2.—*Clinical Findings in Anaerobic Pulmonary Infections*

Clinical Finding	*Frequency (percent)*
Putrid discharge	41
Tissue necrosis	69
Subacute or chronic presentation	57
Suspected aspiration	72
Other predisposing conditions	20

organisms five or ten to one,[1] and in the face of gingival or periodontal disease, the anaerobic microorganisms become even more preponderant; this emphasizes the role of poor oral and dental hygiene as a background for the development of aspiration infection. A reasonably valuable clinical axiom is that lung abscess is uncommon in edentulous persons. In a recent review of lung abscess, in three of four patients with abscesses who were edentulous, bronchogenic carcinoma was ultimately shown to exist and in the fourth there was a subdiaphragmatic abscess that eroded through the diaphragm.[2]

The sequelae of events from aspiration to abscess formation is depicted in Figure 5. Pneumonitis rapidly develops after aspiration. This progresses to three basically different types of involvement. One of these is a lung abscess in which the area of pneumonia cavitates because of the necrotizing potential of the microorganisms. In this circumstance, the organisms and their toxic products actually digest the lung substance and create a hole. Ordinarily, such a cavity would be solitary and rather large, often greater than 2 cm in diameter.

In contrast, necrotizing pneumonia represents an even more severe process despite the fact that the cavities in necrotizing pneumonia are likely to be considerably smaller than those in a lung abscess. Necrotizing pneumonia, the so-called pulmonary gangrene described in preantibiotic days, looks to radiologists and pathologists like Swiss cheese. These patients are generally sicker than those with lung abscess and there is apt to be involvement of multiple lobes instead of the more solitary process of lung abscess. The prognosis is poor and despite aggressive antibiotic therapy, death may occur.

Pneumonitis, lung abscess or necrotizing pneumonia can all extend to involve the pleural space and cause empyema. This is, of course, a special problem that usually requires tube drainage.

It is important to distinguish between nonhospital-acquired and hospital-acquired aspiration infections. Within a few days of admission to the hospital, a transformation of the oral flora occurs with a shift from the usual species toward a larger number of Gram-negative organisms and staphylococci. Therefore, it should come as no surprise that the microflora of abscesses acquired in the hospital differ from those acquired outside: Staphylococcus and Gram-negative organisms occur more commonly in patients with hospital-acquired infections.

From a clinical point of view, a putrid discharge (as in the case reported here) is not present nearly as often as is generally thought. Putrid sputum occurred in fewer than half of the patients in a large series reported by Bartlett and Finegold[2] (Table 2). The fetid odor depends upon the *kinds* of microorganisms that are present. Sputum from anaerobic lung abscesses caused chiefly by Streptococcus, Peptococcus, or Peptostreptococcus does not have a foul odor. It is only when Gram-negative anaerobic bacilli, particularly Bacteroides, are present in large numbers that the characteristic putrid odor develops.

In reported cases, necrosis is present in most; the subacute or chronic manifestations that I have alluded to occur in 57 percent of patients, and conditions that predispose to aspiration can be identified in 92 percent.[2]

When anaerobic infections are suspected, confirmation of the diagnosis is often difficult. Anaerobic cultures have to be processed extremely carefully. The specimens have to be collected in a gas-free tube, and if they are not processed within 20 minutes, they are probably worthless. The source of the material is also very important. Expectorated sputums are not satisfactory because of the high likelihood of contamination by the indigenous anaerobic flora of the mouth and

gingiva. Transtracheal aspiration is the usual technique employed to obtain specimens for anaerobic culture in these conditions.[3] Some clinicians use direct lung puncture. Fiberoptic bronchoscopy must be carried out with meticulous care to obtain adequate specimens for culture. Material obtained by aspiration through the channel of the scope is not adequate because it often reflects contamination by organisms obtained during passage of the instrument through the oropharynx. A catheter carefully placed through the lumen of the scope containing a brush that can be extended for sampling and withdrawn for protection of the sample provides the only truly reliable source. When collected this way, cultures of the material correlate well with those obtained from cultures of transtracheal aspirates. Blood and pleural fluid are good sources of specimens, but blood cultures are not often positive in patients with pyogenic lung abscesses. Pleural fluid is infected only when there is an empyema.

Gorbach and co-workers[4] recently published evidence of increased short chain fatty acid production by anaerobes. Thus early detection of anaerobes by gas liquid chromatography may be possible, although the ultimate clinical value remains to be established.

Usually, two to three species of bacteria are present in a lung abscess.[1,5] The flora include a variety of different organisms, particularly Bacteroides melaninogenicus, Fusobacterium, Peptostreptococcus, Peptococcus, microaerophilic Streptococcus and Bacteroides fragilis. The last microorganism, more commonly found in the abdomen, was present in 10 to 20 percent of the cases and is a worrisome finding because it affects the choice of antibiotics.

In 40 percent of patients with lung abscesses, anaerobes are mixed with aerobic or facultative microorganisms including Diplococcus pneumoniae, Hemophilus influenzae, Klebsiella, Escherichia coli and Staphylococcus. A Gram stain of sputum may be helpful in making the diagnosis. Typically, in patients with aspiration pneumonitis, lung abscess or necrotizing pneumonia, large numbers of polymorphonuclear leukocytes and a quite heterogeneous flora, including Gram-positive and Gram-negative organisms, and cocci and rods are present. The other reason for carrying out a Gram stain is to rule out Staphylococcus or Klebsiella infections, both of which can produce cavitating lesions but are usually associated with a predominant rather than mixed flora. For the same reasons it is important to do an acid-fast stain to rule out mycobacterial infection.

The treatment of choice for anaerobic pulmonary abscesses is penicillin G; high dosages, at least 5 million and preferably 10 million units per day given intravenously, should be administered. High dosages are required because the sensitivity pattern of the microorganisms varies somewhat, and penetration of the antibiotic into the necrotic tissue and abscess fluid may be inadequate at lower dosages.[6] Penicillin is effective, it is cheap, we know its toxic potential and it has stood the test of time. However, in the case reported here the patient clearly did not respond to penicillin and when clindamycin hydrochloric acid was substituted, prompt improvement occurred. The reason for this sequence of events is hard to determine. I carefully reviewed the culture reports, and the only organisms recovered were those mentioned previously. Probably the best explanation for the lack of response to penicillin was the presence of staphylococci or some other penicillin-resistant organism that somehow escaped identification; this would include Bacteriodes fragilis because the Bacteroides that were isolated were not speciated.

Ordinarily, one need not select antimicrobial drugs to encompass the sensitivity spectra of all the bacilli identified. This is an important point. The reason for this may come from some early work on experimental lung abscess: placement of a pure culture of a single microorganism in the lower airways of dogs did not produce an abscess; only when a mixture of organisms was used, did the clinical analogue develop. Therefore, it follows that if antibiotics are effective against most of the organisms, and the number of species is significantly reduced, then the process cannot sustain itself. Alternative drugs for use in penicillin-sensitive patients include clindamycin hydrochloric acid and chloramphenicol. Selection of antibiotics for a patient with a hospital-acquired lung abscess differs and should include antibiotics directed toward the nosocomial spectrum of microorganisms.

The duration of therapy is controversial and empiric. We recommend that high dose intravenous therapy be carried out until the patient is over the acute phases of the illness. The patient should be afebrile, leukocytosis should have abated and a roentgenogram of the chest should show striking resolution of the surrounding infiltrate, diminution in the size of the cavity and

absence of fluid. This usually takes about two weeks. It is then safe to switch to the oral route of administration, as was done in the case reported here. Oral antibiotic therapy should be continued until the cavity wall is thin and the surrounding infiltration has disappeared. This schedule is arbitrary, but is based upon experience that clinical relapse occurs when treatment is stopped too early. The total duration of antibiotic therapy is usually 6 to 12 weeks.

Currently, surgical operation is rarely carried out. If the patient has a residual cavity at the cessation of antibiotic treatment, it will gradually close with time. Massive hemoptysis is an indication for surgical intervention in patients with acute lung abscess. In patients with chronic manifestations, indications for surgical intervention are similar to those for chronic bronchiectasis: resection is done only if recurrent or massive hemoptysis or recurrent infections are present that are disabling to the patient's way of life.

In summary, antibiotics have totally transformed the prognosis of pyogenic lung abscess from a disorder with a mortality of 40 to 75 percent to one with a relatively good prognosis. In the past, patients who did not die were often victims of long-term chronic suppurative sequelae and surgical operation was frequently necessary. Now, well over 90 percent of the patients can be treated successfully by medical means alone. The most important cause of lung abscess, at least in the San Francisco Bay Area, is anaerobic infections. This is especially true when the abscess is acquired outside the hospital. Despite the lack of response in the patient reported here, penicillin remains the drug of choice.

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Informed Consent for New Surgical Procedures

The critical aspect . . . about any new technique is the importance of informed consent. The patient should know something about the procedure and know that the procedure is new. The patient should know something about the potential value of the procedure and why the procedure is being used rather than a standard or an old procedure, which once was used for the same thing. The early or long-term results should be discussed and the patient should be given some choice in the use of the new technique or an older one. . . . The difficulty, I think, is when you get into new surgical procedures where you are doing a prospective study of one or more procedures and where the surgeons and physicians involved do not know which of the two procedures might be better. In this situation, we do not know which is the best procedure and we have to try to explain this to the patient, remembering the principle of medical ethics: . . . that a patient who is to receive an investigational drug shall be told the nature, purpose, and possible side effects of the drug . . . .

—ROBERT E. HERMANN, MD, *Cleveland*

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Important Advances in Clinical Medicine

Epitomes of Progress—Internal Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Internal Medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Internal Medicine which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Internal Medicine of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Sick Sinus Syndrome

THE SICK SINUS SYNDROME is a malfunction of the sinus node progressing at an uncertain rate characterized primarily by sinus bradycardia at rest and a disproportionately slow rate with exercise, fever or excitement. There is often associated failure of normal "escape" pacemakers as well, and asystole may develop when sinus arrest or sinoatrial block occurs.

The cause of the disorder is often ischemic and may occur spontaneously or after a coronary occlusion that involves the sinus node artery. It can also be caused by myocardiopathies, collagen diseases and rheumatic, infiltrative and irritative lesions.

The syndrome usually occurs in older persons but no age group is exempt. The symptoms are related to impaired perfusion of vital organs and can range from acute pulmonary edema or sudden loss of consciousness (Stokes-Adams attacks) to weakness, forgetfulness and a reduced exercise tolerance.

With such nonspecific symptoms, a physician must have a high index of suspicion; not all sinus bradycardias are benign. Findings on long-term electrocardiographic monitoring often are diagnostic, particularly if associated with symptoms. The tracing may show unusually slow rates with or without escape rhythms, or rapid rates such as paroxysmal atrial tachycardia and atrial fibrillation, or both slow and rapid rates. When both slow and rapid rhythms are present, it has been called the brady-tachy arrhythmia syndrome. The most helpful provocative test is to see how long it takes the sinus node to recover after atrial pacing. Normally the pause before the next beat is less than 115 percent of the resting control rate. If it is longer than 120 percent, the sinus node is sick.

Sinus bradycardia due to a sick sinus will speed up only slightly with intravenous administration of atropine or isoproterenol (to less than 90 to 100 beats per minute) and drugs such as digitalis or propranolol given to control the rapid rates will depress the sinus node (and atrioventricular node) still further. The treatment of choice is use of a permanent demand pacemaker. The treatment of the underlying heart disease must not be neglected, and is facilitated with use of the artificial pacemaker.

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Therapy of Viral Encephalitis

BETWEEN 1,500 and 3,000 cases of encephalitis are usually reported to the Center for Disease Control in Atlanta each year. In most of these patients no specific etiologic diagnosis can be established; however, postinfectious states, arboviruses and herpes simplex virus account for most of the identifiable causes. The outcome of these illnesses is variable, and depends at least in part on the infecting virus and the age of the patient; however, beween 5 and 10 percent of patients with viral encephalitis die and a less certain percentage are left with permanent neurological disabilities. Because of these hazards there exists considerable interest in the development of some form of effective treatment. The devastating effects of herpes simplex encephalitis (mortality rates between 25 and 50 percent) combined with the availability of several chemotherapeutic agents with *in vitro* efficacy against this virus has led to a number of clinical investigations utilizing these drugs. To date, idoxuridine has been established to be more harmful than beneficial and cytosine arabinoside, which also possesses major toxic effects, has been found to be of questionable value at best. Poly I:C (a complex nucleotide, synthetic polyinosinic-polycytidylic acid), an effective interferon inducer, has also been tried but offers little hope because of its adverse effects. Adenine arabinoside is currently being tested, and the question of its effectiveness awaits the outcome of controlled studies.

No specific therapy is available for arboviruses, but interferon and its inducers have been shown to be effective against experimental arbovirus infections when given before or shortly after the administration of virus. No extensive clinical trials of the substances have been undertaken.

Lastly, postinfectious encephalitis, usually associated with mumps, measles or chicken pox, may well be mediated in many cases by conditions other than direct viral invasion of the brain. Many investigators feel immunological phenomenon may be important in these disease processes. No antiviral agent has been shown effective in these disorders.

THOMAS C. CESARIO, MD

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Mitral Valve Prolapse

MITRAL VALVE PROLAPSE is the most common cause of mitral regurgitation. Although prolapse may result from or be associated with Marfan's syndrome, ischemic heart disease, atrial septal defect and hypertrophic cardiomyopathy, there is no identifiable cause in most involved patients. Myxomatous degeneration of the mitral (and occasionally the tricuspid) valve is commonly present in this syndrome.

Auscultation of a variable midsystolic click or late systolic murmur, or both, strongly suggests the diagnosis. Examination during postural maneuvers may intensify or clarify the pathological findings. When the patient squats, the click moves toward the second sound and the murmur is abbreviated and softened. Standing after squatting moves the click toward the first sound, and greatly intensifies and lengthens the murmur.

Most patients are asymptomatic. However, there is a subset of subjects with mitral valve prolapse in whom both symptoms and associated abnormalities are present. A clinician should suspect prolapse when confronted with a young, often anxious, thin patient complaining of fatigue and chest pain or palpitations, or both. Women outnumber men two to one among these patients. Bony abnormalities such as kyphoscoliosis, pectus excavatum and "straight back syndrome" are common. On electrocardiograms, inferior lead T wave inversion, prolonged Q-T interval and frequent atrial or ventricular premature beats may be seen. Exercise may cause ST segment depression and increase the frequency of premature beats, especially after the exercise. Rarely, a life-threatening arrhythmia such as ventricular tachycardia occurs; ventricular fibrillation and sudden death have been reported.

Findings on echocardiography may be diagnostic, showing there to be systolic posterior excursion of one or both mitral leaflets. Cardiac catheterization is rarely indicated for diagnosis, but if the characteristic leaflet billowing is shown to exist and coronary arteries are judged by angiography to be normal, these may help establish that coronary obstruction is not causing the patient's chest pain.

Antibiotic prophylaxis is indicated for dental or potentially contaminated surgical procedures. Propranolol, 40 to 320 mg per day, should be used for symptomatic or life-threatening arrhythmias. Refractory ventricular arrhythmias have

been controlled by atrial overdrive pacing and mitral valve replacement.

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Treatment of Myxedema and Myxedema Coma

EXCEPT FOR myxedema coma, there are few situations in which hypothyroidism requires rapid restoration of the eumetabolic state. Hypothyroid patients are sensitive to thyroid hormone replacement, even at low doses and, therefore, therapy should be initiated at a dosage of no more than 50 μg of levothyroxine per day. In patients with underlying heart disease or severe hypothyroidism the initial daily dose should be even lower. The dose should then be increased by 25 to 50 μg at two- to four-week intervals until a normal metabolic state is reached. The final maintenance dose should be approximately 200 μg per day.

Occasionally, cardiovascular or psychiatric complications limit the use of the full therapeutic dose and replacement therapy must be modified to attain the maximal metabolic state without adverse effects.

The clinical state of the patient is generally the best determinant of adequate thyroid hormone replacement. The wide range of normal for thyroxine (T_4) concentration makes the T_4 determination useful only as a confirmation of a patient's metabolic state. In a patient with thyroprival hypothyroidism, thyroid-stimulating hormone (TSH) determinations can be used to assess the patient's response to thyroid hormone replacement.

Although levothyroxine appears to be the agent of choice in replacement therapy of hypothyroidism, for those who prefer other agents the equivalent doses are levothyroxine, 100 μg; liothyronine, 25 μg, and thyroid extract, 60 mg.

The severity of myxedema coma requires that the diagnosis be made clinically and therapy begun immediately. Therapy should be initiated with 400 to 500 μg of levothyroxine given intravenously. Respiratory care is critical and hypoventilation should be treated by assisted ventilation and controlled oxygen administration. The occasional associated hypoglycemia should be treated with concentrated glucose solutions to avoid water intoxication. Dilutional hyponatremia should be treated by water restriction but may occasionally require hypertonic saline infusion. Hydrocortisone, 100 to 200 mg per day, should be administered intravenously. The patient should not be actively warmed. Precipitating factors such as infection should be sought and treated.

Although myxedema coma generally has a poor prognosis, a regimen such as the above, especially with critical attention to respiratory care and ideally in the setting of an intensive care unit, should increase survivals.

ITAMAR B. ABRASS, MD

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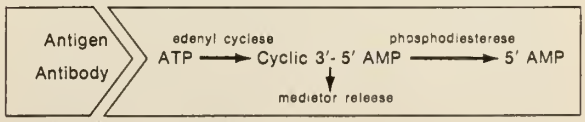
Bronchodilator Pharmacology

ALTHOUGH A VARIETY of catecholamine and xanthine preparations have been used for the treatment of asthma and other types of airway obstruction for many years, only recently has the mechanism of action of these agents become appreciated. An understanding of bronchodilator pharmacology has led to the rational use of these agents and has given impetus to the search for additional agents with greater specificity of action.

The airway obstruction of acute bronchial asthma is due, at least in part, to the release of several biologically active substances, as shown in a simplified diagram in Figure 1.



AMP = edenosine monophosphate
ATP = edenosine triphosphate

Figure 1.—Diagram showing release of biologically active substances.

Intracellular biochemical events are initiated by an antigen-antibody reaction on the cell surface, leading to a release of a variety of mediator substances. The level of cyclic adenosine monophosphate (AMP) inversely determines the amount of mediator release. Increased cyclic AMP leads to less mediator release and less bronchospasm, and decreased cyclic AMP leads to increased mediator release.

Among the agents that stimulate cyclic AMP formation, via the enzyme adenyl cyclase, are the beta-adrenergic stimulator agents (isoproterenol, metaproterenol, isoetharine and ephedrine), parasympathetic nervous system inhibitors and alpha-adrenergic blocking agents. A subgroup of beta-adrenergic agents (called beta-2) have primarily a bronchodilator action with minimal cardiac activity. The level of cyclic AMP can also be increased by decreasing its breakdown by the enzyme phosphodiesterase. The methylxanthines (theophylline) act by this mechanism.

The effects of beta-adrenergic agents (for example, isoproterenol) and the phosphodiesterase inhibitors (for example, theophylline) are synergistic, so that treatment with both of these classes of pharmacologic agents will result in less mediator release and less bronchospasm than one group alone.

The release of mediators may be prevented in some persons by administration of cromolyn sodium, even after the antigen antibody reaction has taken place.

Coincident with the biochemical information elucidating the method of action of bronchodilator agents have been studies of the dose response curves of theophylline preparations, correlating relief of airway obstruction with the serum levels of theophylline. Aminophylline, a salt of theophylline, given intravenously in a dose of 5.6 mg per kg of body weight as a loading dose and 0.9 mg per kg per hour as a maintenance dose, gives good plasma levels and bronchodilator activity in a large percentage of patients. There are also good studies available concerning the dose response of oral theophylline preparations.

Information is also available on the dose response curves of a variety of catecholamines given by aerosol (metaproterenol, isoetharine, isoproterenol, epinephrine). In addition, the beta-adrenergic agents metaproterenol and terbutaline are now available for oral use. Other agents are undergoing clinical trial and will, it is hoped, soon be available for clinical use.

An understanding of the pharmacology of bronchodilators can replace empiric therapy.

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Gastrointestinal Endoscopy

ADVANCES IN gastrointestinal endoscopy have been rapid and dramatic since the development of flexible fiberoptic instruments in the late 1950's. The upper gastrointestinal tract to the level of the ligament of Trietz may now be inspected with a single instrument. In addition, cytological specimens may be obtained with the use of a brush or a pulsating jet of fluid introduced through a special channel in the endoscope, or a forceps may be introduced through the channel and a direct biopsy specimen taken. The instrument has also been utilized for therapeutic procedures, such as removal of gastric polyps, foreign bodies or retained sutures and arrest of bleeding by means of electrocoagulation or a laser beam.

An additional benefit is the ability to apply still photography and cinematography. In some centers, images are projected onto a television screen, thereby permitting viewing at a site remote from where the actual procedure is carried out. Detection of bleeding sites with endoscopy employing ultraviolet light after intravenous injection of fluorescein represents still another newer adaptation.

Endoscopic retrograde cholangio-pancreatography (ERCP) is now possible through the use of a side-viewing fiberoptic duodenoscope. A catheter introduced through the duodenoscope is inserted into the papilla of Vater under endoscopic guidance. Radiographic contrast material is then injected through the catheter and roentgenograms exposed to show the biliary or pancreatic ductal systems, or both. This nonoperative technique is of particular value in puzzling cases of jaundice and in the detection of pancreatic disease.

A long (165 cm) fiberoptic colonoscope is widely used today to visualize the entire large bowel. Through this instrument, biopsy specimens may be taken, cytological specimens obtained and polypoid lesions removed or destroyed by fulgur-

ation. As a consequence, it is unnecessary now in many cases to resort to laparotomy and colotomy to remove colonic polyps well above the reach of the conventional proctosigmoidoscope.

It should be emphasized that the newer endoscopic instruments and the diagnostic and therapeutic maneuvers that may be carried out with them require great skill, training and experience. They must be used judiciously for they are not without some hazard. Properly employed and with appreciation of their limitations, much may be accomplished and still more may be confidently anticipated as further diagnostic and therapeutic advances are made in this field.

DANIEL PELOT, MD

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His's Bundle Electrocardiogram

THE STANDARD surface electrocardiogram, though very useful, is limited in evaluation of function of the specialized conduction fibers such as the atrioventricular (A-V) node, His's bundle, bundle branches and Purkinje's fibers. The P-R interval on an electrocardiogram is the sole representation of electrical activity in all these fibers.

His's bundle electrocardiography allows the more precise localization of the site of conduction abnormalities and the analysis of various arrhythmias. This increased accuracy is useful in determining prognosis as well as appropriate therapy.

A multielectrode catheter is passed under fluoroscopic control via a percutaneous femoral or antecubital approach across the tricuspid valve into the right ventricle. Electrical activity is recorded from the right atrium (A), His's bundle (H) and ventricle (V). The H deflection is a sharp biphasic or triphasic spike recorded between the A and V deflections. The P-R interval, therefore, is subdivided into A-H and H-V intervals, which represent conduction through the A-V node and His-Purkinje system respectively. Simultaneous atrial pacing may provide additional information about the entire A-V conduction system.

The decision to place a temporary or permanent transvenous pacemaker is aided by knowing:

- If there is prolongation of H-V interval (>120 milliseconds), as this carries often a more serious prognosis (development of complete heart block)—prolongation of the A-V interval (>55 milliseconds) has less serious implication;
- If bifascicular or trifascicular blocks are masquerading as simpler conduction defects on the surface electrocardiogram, and
- If an advanced atrioventricular block is due to digitalis alone or disease alone, or both.

His's bundle electrocardiography is also valuable in the differentiation of premature ventricular contractions from aberrant conduction, ventricular from supraventricular tachycardia with aberrant conduction or bundle branch block, suspected preexcitation syndrome (Wolff-Parkinson-White syndrome) and the sick sinus syndrome.

It is well to remember that pharmacologic and physiologic modalities influence A-V conduction intervals. The A-H interval is prolonged by atrial pacing, atrial premature beats and administration of propranolol, digitalis or lidocaine, and shortened by administration of isoproterenol, atropine and, variably, diphenylhydantoin. The H-V interval usually remains unaffected but is prolonged by procaineamide administration.

PIETER VANDENHOVEN, MD

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Giardiasis

GIARDIA LAMBLIA is becoming increasingly recognized as a pathogen. It has been identified as a causative organism in epidemic diarrhea and in the diarrhea of travelers. Epidemics have been reported from Portland, Oregon, and Aspen and Boulder, Colorado. The attack rate in visitors to Leningrad is more than 30 percent. This is an underestimate since the diagnosis often depended upon the examination of one stool. The parasite is also prevalent in the Mediterranean countries.

In contrast to the usual traveler's diarrhea due to enteropathic Escherichia coli, the incubation period is long (one to eight weeks). The victims frequently do not become ill until they return home. The usual symptom is diarrhea, frequently with malabsorption, and weight loss. Nausea,

vomiting, anorexia and abdominal bloating may also occur.

The diagnosis may be made on examination of several stools. Patients not having diarrhea usually pass only cysts. Trophozoites appear only in patients having significant diarrhea. Stool examination is an insensitive means of establishing the diagnosis. The most sensitive methods are duodenal intubation, small intestine mucosal biopsy and gently smearing the mucus on the biopsy onto a slide. The slide is air-dried and stained with Giemsa stain.

The pathogenesis of symptoms in giardiasis is not defined. A number of phenomena have been observed. These include epithelial and mucosal invasion, reversible disaccharidase and vitamin B_{12} and folate malabsorption.

The organism has been shown to deconjugate bile acids in the absence of bacterial overgrowth. Patients with gastrointestinal immunodeficiency diseases have a peculiar susceptibility to Giardia infection. Diarrhea and malabsorption in these patients is almost always due to this organism.

Giardiasis should always be treated when identified, even in asymptomatic patients. Between 80 and 90 percent of infections may be cured with administration of quinacrine, 100 mg three times a day, for one week. Repeat courses are occasionally required. Metronidazole (Flagyl®), 750 mg three times a day for ten days, is an excellent alternative drug. This drug is an investigational new drug for this purpose in the United States.

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Clindamycin-Associated Colitis

REPORTS OF UNTOWARD EFFECTS from oral and intravenous therapy with clindamycin noting severe and even fatal complications have abounded in the literature in the last two years. Affected patients report abdominal cramps and watery diarrhea, with or without hematochezia or passage of mucus. These symptoms can occur within one day of therapy and as long as several months after stopping administration of the drug, as reported in a number of recent articles. Typical findings of clindamycin-associated pseudomembranous colitis at sigmoidoscopy consist of mucosal friability, with interspersed raised creamy, yellowish plaques. Findings on rectal biopsies have shown inflammatory changes with mucosal destruction, fibrinoid necrosis and a prominent pseudomembrane (pseudomembranous colitis). Colonoscopy showed these changes to extend beyond the surface routinely surveyed at sigmoidoscopy, and using barium enemas it was shown that the inflammatory changes can involve the entire colon.

What makes clindamycin-induced pseudomembranous colitis so dangerous is its frequent unresponsiveness to routine therapeutic measures. Administration of diphenoxylate hydrochloride (Lomotil®) and kaolin powders (Kaopectate®) often brings no relief and may in fact, as stated in one package insert, "prolong or worsen the condition." Use of steroids, though recommended by some, offered no significant improvement to the patients observed. Recently Burpige and Milligan have advocated the use of cholestyramine as having proved beneficial in two cases they have studied. This is welcome information and if corroborated would make cholestyramine the first useful medication against the dreaded complication, but this needs to be further documented.

The best way to reduce the incidence of clindamycin-associated colitis is to limit the use of clindamycin to its proper indications. It should never be used as a routine medication except

- As an alternative drug in patients with staphylococcus aureus infections who cannot tolerate penicillin or cephalosporin,
- In the management of suspected or proven severe infections due to Bacteroides fragilis and
- In the initial management, pending bacteriological results, in acute peritonitis following perforation of a viscus.

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Candida Septicemia

INVASION OF THE bloodstream by Candida organisms occurs most frequently in patients in hospital in whom prolonged intravenous catheterization has been required. Especially susceptible are patients with burns and those given intravenous antibiotics or parenteral hyperalimentation. In such cases Candida organisms from the skin or possibly the bowel colonize the catheter tip and surrounding vein, creating a nidus for continuous hematogenous infection. Drug addicts may infect their veins by injecting material contaminated with Candida organisms, and, rarely, in an uncontrolled diabetic candidemia develops when bladder thrush extends to the renal pelvis and invades the papillae.

Candida septicemia is heralded by fever and occasionally by hypotension and confusion, so that it may be mistaken for Gram negative bacteremia. The fluffy white exudates of Candida chorioretinitis provide a helpful clue when present. A urine smear showing Candida organisms offers supporting but by no means conclusive evidence. Candida organisms grow readily in routine blood culture media but a presumptive diagnosis of candidemia can be made immediately if a colony of yeast is found on direct smear of a catheter tip. The recent discovery that Candida albicans septicemia in man can be detected by gas-liquid chromatography of serum has provided a promising rapid diagnostic tool. By the use of this technique, which identifies breakdown products of yeast cell wall sugars, cases of candidemia have been identified and treated several days before the blood cultures turned positive.

Candidemia usually resolves within a few days after removal of a contaminated catheter unless a new one is inserted immediately in its place. Frankly purulent veins should be excised. More vigorous treatment is required if fever and fungemia persist, if azotemia or metastatic abscesses develop, or if cardiac valvular disease is present. In such cases both amphotericin B and 5-fluorocytosine (5-FC) should be given until 5-FC sensitives are determined, since some strains of Candida organisms are resistant to 5-FC. Infected cardiac valves generally must be replaced.

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Plasma Calcitonin Measurement As a Marker for Cancer

THE MEASUREMENT of plasma calcitonin by radioimmunoassay can serve as a marker for the diagnosis of certain types of cancer. The value of this procedure is best documented for medullary thyroid carcinoma, a tumor that can occur sporadically or on a familial basis, usually as part of a multiple endocrine adenomatosis (MEA Type II). This tumor occurs in the calcitonin-secreting cells of the thyroid gland, and in patients with medullary thyroid carcinoma, therefore, abnormally high plasma levels of calcitonin are found. In most patients with this tumor, the diagnosis can be established by the relatively simple measurement of an abnormally elevated plasma calcitonin level by radioimmunoassay. However, in some patients basal calcitonin levels are indistinguishable from normal, and provocative infusions of calcium or gastrin are necessary to produce diagnostic elevations of the hormone.

Selective venous catheterization in combination with calcitonin immunoassay can help to define the extent and location of the tumor and serial hormone measurements can be used to monitor therapy. Early application of these procedures can result in diagnosis of cancer while it is still confined to the thyroid gland and potentially curable by thyroidectomy. This consideration is especially important for screening the relatives of an affected patient since the syndrome is inherited on an autosomal dominant basis. Therefore, the diagnosis in one patient often leads to the early diagnosis of unsuspected tumor in relatives of the patient.

Recent studies suggest that there may be a wider diagnostic application of the calcitonin assay. Some thyroid tumors that do not have the classical histological pattern of medullary thyroid carcinoma also seem to produce abnormal amounts of calcitonin. Therefore, measurement of the hormone may be diagnostically useful in other types of thyroid cancer. Perhaps of greater potential importance is the observation that several nonthyroid tumors can ectopically produce abnormal concentrations of calcitonin. Therefore, calcitonin radioimmunoassay may have even wider clinical application in the diagnosis of cancer.

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Surveillance in Hospital Infection—What Should be Cultured?

INFECTION CONTROL should regularly use limited surveillance. Additional routine microbiologic surveillance has not helped in prevention or control of nosocomial infections. Significant to the hospital is the patient—not the microbiologic flora unless it is shown to be the probable cause of hospital infections.

The first technique, surveillance for hospital infections including appropriate microbiologic cultures, should be done regularly to identify infectious problems at their onset when antecedent factors can be evaluated for causual relationships. Epidemiologic investigation is the most efficient means of confirming the problem and identifying reservoirs and transmission for the organisms. Cultures can confirm the relationships implicated by an epidemiologist. After resolution, repeat culture should show the effectiveness of corrective procedures. (Careful monitoring to be certain the procedure is done properly, not routine microbiologic surveillance, should be the follow-up method.)

Established hospital procedures, including isolation, antimicrobial treatment of infected patients, appropriate care of bladder catheters and intravenous infusion sites may curtail most nosocomial epidemics. Only a small percentage of epidemics can be predicted by environmental cultures; most are never detected. The usual reservoirs or modes of transmission for pseudomonas, klebsiella, proteus, providence and other serious nosocomial and opportunistic organisms are unknown. We do not know where to culture. Experience says only when routine cultures are of little value. Although environmental sampling will find potential pathogens, the significance of this information is not clear—there are no accepted standards. Therefore, the results are not interpretable.

As a second surveillance technique, routine microbiologic sampling of sterilizers (autoclaves more frequently than every month and gas sterilizers at least every week) is of established value. Routine microbiologic sampling to monitor disinfection and housekeeping is less valuable than monitoring to prove they were done properly.

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EDITORIALS

A BICENTENNIAL EDITORIAL ESSAY

"We Hold These Truths To Be Self-Evident"

"We hold these Truths to be self-evident, that all Men are created equal, that they are endowed by their Creator with certain unalienable Rights, that among these are Life, Liberty, and the Pursuit of Happiness—That to secure these Rights, Governments are instituted among Men, deriving their just Powers from the Consent of the Governed . . . ."

—FROM THE DECLARATION OF INDEPENDENCE, 1776

IT IS NOW exactly 200 years since the above words were being written. They have profoundly influenced this great nation and there is reason to believe that they are responsible to a considerable degree for America becoming the great nation that it has. But it is curious that even after 200 years none of these "self-evident truths" has yet become a truly workable reality in America. It therefore seems appropriate to examine them in light of where we are today. Previous editorials in this bicentennial series have addressed some of the ways these "self-evident truths" are now being viewed both by society as a whole in America and in the context of health care—where so many of the technologic, social, economic and political problems of the day seem to be coming into focus.

The series began in January by drawing attention to quality of life as a possible new goal for America and also to the fact that technology, industry, and the social, economic and political institutions of America have become progressively and irreversibly interdependent. The suggested goal—quality of life—is perhaps a semantic refinement of life, liberty and the pursuit of happiness, but it is also a term that is coming into more frequent use in health care and elsewhere, and therefore merits more discussion and more precise definition. This will be addressed in a special symposium on "Medicine and Quality of Life" in the July issue of this journal. The reality of interdependence—and worldwide technologic, social, economic and political interdependence in a closed biosphere at that—certainly was not and could not have been foreseen by those who wrote and signed the Declaration of Independence in 1776. In 1976 interdependence is not only with us but it is gradually moving in on independence. The basic truth of this interdependence and its relationship to necessary governance and regulation of independent and yet interdependent technologic, social, economic and political systems thread through the editorial discussions that have comprised this series. It so happens that each one has, tangentially at least, addressed one of the "self-evident truths" that were proclaimed in the Declaration of Independence.

The concept that "all men are created equal" seems to find expression in today's egalitarianism. This was considered in "The Professional in America Today" [February], where it was suggested that today's egalitarianism is not rooted in any social or biological truth, and that the reality of the social and biological uniqueness of every person, and the right of each to at least some degree of personal fulfillment (or quality of life) will of necessity displace the unreality of today's egalitarian approach to almost every aspect of life. The idea that all men are created equal for purposes of equal treatment and equal justice under the law is fair and true, and no doubt what was intended by the signers of the Declaration of Independence. But this is not to be confused with assuming or trying to mandate equality in the lives and experience of individual persons—which seems to be the goal of today's egalitarianism, and which is not only unrealistic but is antisocial and antibiological as well.

The idea of "rights" seems also to have evolved beyond what the signers of the Declaration of Independence are likely to have had in mind. This was addressed under the title "The Growing Dimensions of Professional Injury Liability" [March]. Here the idea of rights, and perhaps the idea of a right to life, liberty and the pursuit of happiness, appear to have been extended to include a right to freedom from personal risk, and when some injury or damage has occurred, to the right to some kind of compensation or redress, usually monetary. The enormity of the economic

impact of this first surfaced in medicine's professional liability crisis a year ago, but now is appearing elsewhere. Bar owners recently have had their liability insurance premiums quadrupled, an effect of courts holding them responsible and liable for any misadventure a patron may have as a result of indulgence at their bar. Even more recently, the Chief Justice of the United States is reported to have called for changes in the tort system of law because of these inimical trends which not only threaten to overwhelm the courts but to bankrupt society as well.

The "self-evident truths" of equality, of rights, and of life, liberty and the pursuit of happiness now seem to be producing fundamental change in America, in a sense almost another American revolution 200 years after the first. Under the heading "America in Process of Change" [April] attention was called to the new entitlements that are now beginning to be considered rights—entitlements to housing, income, education, health, as well as to a certain freedom from personal risk and to a degree of personal fulfillment or quality of life. It is almost as though we were developing a new social ethic, with the individual person as the center of the stage, to replace our traditional economic ethic with economic growth and material gain at the center of the stage. This is disturbing to many but it could be the beginning of a bold, new exciting era for America—perhaps even a new era of leadership in the world of today and tomorrow.

The last "self-evident truth," "government . . . with the consent of the governed," was considered in an editorial "On the Governance of Health Care" [May]. Here governance was viewed as independence within a framework of interdependence, and the problem compared with the governance of a biological system—which is what not only health care but modern society really is. It was suggested that the idea of "with the consent of the governed" needs strengthening in today's society. It just is not enough to say that government is simply established with the consent of the governed and then it is free to govern as it pleases. Adolph Hitler was voted into power with the consent of the governed in this sense. The consent of the governed should clearly be a continuous process and should somehow include the consent of any specific groups in society who are to be ruled or regulated, as well as the public at large for whose benefit the regulations are presumably made. It is just as important that the "self-evident truths" apply to the governed and regulated minorities (such as those who provide health care, for example) as that they apply to anyone else. The mechanisms to accomplish this in practice have yet to be devised, but at issue is the fundamental question of whether the government is to be the master or the servant of the people, the same issue that brought about the American revolution.

The "self-evident truths" as set forth in our Declaration of Independence 200 years ago are an integral part of America's past and will be an integral part of its future. They are essential stepping stones toward achieving the best possible for human life on this planet. But they are no longer freestanding truths, if they ever were, in the sense that they are independent of other reality. And two such other realities or truths are (1) the biological nature of man and of human society and (2) the growing technological, social, economic and political interdependence of humanity on this earth, whether one is speaking of health care, human society as a whole, or whatever. These two truths, and no doubt others, will also have to be taken into account before the "self-evident truths" of the Declaration of Independence can ever become truly workable realities in America. It is evident enough that much of this will come to a head in health care. Indeed it already has.

—MSMW

Male Hypogonadism

THERE IS EXTRAORDINARY redundancy built into the reproductive pattern of the human male. To avoid overrunning the planet, we are enjoined to have only two or three children. Yet in a lifetime, a man can produce as many as 10^{15} spermatozoa. As in many endocrine systems, there is also a significant quantitative reserve in production of the relevant hormones; that is, we *can* make much more hormone than we do. Finally, there are critical elements of timing—certain testicular capacities must be exercised during one particular week of intrauterine existence, while others are irrelevant in childhood but irreplaceable to adults. Given these diverse roles for the testis, it is no surprise to find a complex set of controls and a wide

range of disorders of testicular function. It is a pleasant surprise, however, to see their current understanding as clearly and concisely outlined as Odell and Swerdloff have done in this issue's medical progress section.

The earliest known function of the testis is that of virilizing the male fetus *in utero*. This function of the testis as an embryonic organizing force becomes apparent in the first trimester of gestation. Sexual differentiation requires differential development of at least three organs—brain, breast and genitalia. But these structures are not genetically determined as either male or female. Rather, all mammalian embryos are capable of both male and female differentiation: in the absence of a testis, development proceeds along female lines; when present, a testis directs male differentiation. Two testicular products, a protein (not yet isolated or characterized) and a steroid (testosterone) are needed for these events to occur. The protein inhibits development of female genital primordia, and hence is known as müllerian regression factor. The steroid fosters the male ducts, and an intracellular metabolite of testosterone virilizes the external genitalia.[1,2] There are now distinct heritable syndromes involving (1) absence of the müllerian regression factor, (2) defects in testosterone synthesis or (3) defects in response to testosterone. All of these result in the several types of male pseudohermaphroditism, raising challenging problems of sex assignment and rational therapy.

Adult male reproductive function is basically a three-level system. Beginning with puberty, there is a sequential activation of central nervous system (CNS), pituitary and testis which results in both hormone biosynthesis and spermatogenesis. Many areas of the CNS play facilitative or inhibitory roles, but the final channeling is at the hypothalamus, which produces the releasing hormone that directs the synthesis and release of gonadotropic hormones by the pituitary. Two gonadotropins are known to be active in man—follicle stimulating hormone (FSH), which acts predominantly on the seminiferous tubules, and luteinizing hormone (LH, or interstitial cell stimulating hormone, ICSH), which acts predominantly on the Leydig cells to activate steroid biosynthesis. LH works in the pattern now known to be typical of many of the peptide and glycopeptide hormones, by stimulating adenyl cyclase and increasing the intracellular cyclic AMP level. The mechanism of action of FSH has been much more elusive, however, but current evidence suggests that its major role may be to increase "access" of testosterone to its site of action in the tubule, by increasing tubule permeability to the hormone as well as by stimulating the formation of an androgen-binding-protein receptor. Testosterone plays a crucial role in spermatogenesis and is, of course, the primary source of male secondary sex differentiation and of the maintenance of adult male libido and potency.

Defects in this system can occur at any level. Failure to produce the releasing hormone or the pituitary gonadotropin, or inability of the testis to respond to appropriate stimulation can each result in hypogonadism. There are now sensitive assays for both the gonadotropins and the circulating steroids. In addition, there are pharmacologic approaches to challenging the system at all three levels. Clomiphene is an estrogen analogue which triggers release of the hypothalamic gonadotropin-releasing hormone. The latter, known as GnRH, is also available. Thus if one has a hypogonadal patient with low gonadotropin levels, judicious use of these agents may pinpoint the site of the lesion. Similarly, the LH-like chorionic gonadotropin is available to challenge testicular secretory reserve. Using these tests, as clearly outlined in the review, it is possible to made a precise diagnosis in almost all patients and, if the lesion is central, to offer specific therapy.

What remains to be done? There are still many points to be worked out in the laboratory. The world as a whole is threatened by overpopulation, and a better understanding of male reproductive biology might lead to improved methods of population control. But there is also a crucial role for clinicians. Hypogonadism takes a serious, if often silent, toll in human satisfaction and fulfillment. Alert recognition, precise diagnosis, unembarrassed interpretation and specific therapy can bring enormous satisfaction to affected persons and to caring physicians.

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Fighting Back

It is good to see physicians who have been the victims of unjustified and unjustifiable law suits beginning to fight back. They are suing lawyers or others who sued them or who included them in malpractice suits when there was no legitimate basis for claiming the physicians contributed in any way to the injury the patient alleged. And there has been some success. A pathologist in southern California was awarded a $10,000 settlement of a countersuit for malicious prosecution —where his only involvement in the case was that he did the autopsy on the deceased patient. The attorney had refused to dismiss the action against the pathologist until some seven years after the alleged injury occurred—an injury for which the pathologist could not possibly have had any responsibility.

Several state and county medical associations are helping their members in counterattacks against attorneys in selected cases when there have been frivolous or malicious suits against physicians. The California Medical Association, by an action of its House of Delegates in February, undertook to help physicians in some of these cases with legal research and other support when warranted. In Illinois, legal assistance in selected cases is available from the Illinois State Medical Society to the attorney of a member physician who wishes to file a countersuit. The Iowa Medical Society is in the process of developing a similar program, and there are county societies in Florida, Georgia and Texas that are providing such assistance.

It is becoming increasingly evident that physicians and the medical profession are going to have to fight many of their battles in the courts, not only in their own behalf, but in the interests of their patients and the public as well. (The California Medical Association itself has gone to court in the past—and won—in behalf of patients and the public.) This is working within the American system, and medicine has as much at stake as any other segment of our society in making the American system work. Plaintiffs in malpractice lawsuits and their attorneys who have for so long demanded that their claims be submitted to and resolved by a jury may now expect to find their own conduct subjected to jury review.

—MSMW

Lung Abscess

The case presented in the Medical Staff Conference on lung abscess in this issue is of distinct interest. Unique features include hilar adenopathy and resistance to therapy that is ordinarily effective. Differential diagnosis would include fungus infection, tuberculosis and tumor. Presence of an aspirated foreign body must always be considered, as well, in any case of lung abscess. Appropriate workup ruled out these possibilities. Moreover, there was evidence to indicate that the process was an anaerobic infection and mediastinal adenopathy may be seen with this type of infection on occasion. The fetid odor to the sputum is a definitive clue to involvement of anaerobic bacteria in the infection, provided necrotizing gingivitis or other intraoral anaerobic infection which might impart such an odor to coughed sputum can be ruled out. When the latter type of infection is present, foul or putrid odor of material obtained by transtracheal aspiration establishes the role of anaerobes in the lung abscess. The absence of aerobic bacteria on culture would indicate that the infection was purely anaerobic. As noted by Dr. Murray in the staff conference, absence of a fetid odor does not exclude the possibility of an anaerobic infection since some anaerobes do not produce the offensive volatile products accounting for the odor and since some pulmonary lesions do not communicate with a bronchus.

Other features suggesting anaerobic infection, as summarized by Dr. Murray, include aspiration, the prolonged course of the illness, tissue necrosis, and dental or gingival disease. Although there was no history of unconsciousness or aspiration, the likelihood of aspiration is great in a person with disorientation and catatonic behavior in whom a lung abscess develops in a dependent pulmonary segment (the apical-posterior segment of the left upper lobe). Although anaerobic pulmonary infection may be acute and fulminating, most of such infections run a subacute or chronic course. This is relatively unique among bacterial pulmonary infections. Tissue necrosis may result in lung abscess, usually solitary, as in the patient discussed, or may be in the form of multiple, small excavations (necrotizing pneumonia) in which case the prognosis is much poorer.

Periodontal disease, gingivitis and other dental conditions involving anaerobes are important

background factors for anaerobic pulmonary infection. Unfortunately, many physicians are not familiar enough with dental pathology and describe abnormalities of various types in very general terms (such as "poor dental hygiene" or "poor dental repair") which are meaningless. Anaerobic bacteria do not play a role in the usual type of caries seen in children, but anaerobes may be important in root, pit or fissure caries and in acute necrotizing ulcerative gingivitis, the various stages and forms of periodontal disease, root canal infection and periapical abscess. Additional clues indicating possible involvement of anaerobes include the unique morphology of certain anaerobes on Gram stain of transtracheal aspirate or empyema fluid and failure to obtain likely pathogens on conventional culture of appropriate specimens.

In a prospective study of 26 cases of primary lung abscess,[1] anaerobic bacteria were recovered in 24 (92 percent) and in two thirds of these patients, anaerobes were the exclusive isolates. Thus, lung abscess is primarily an anaerobic infection. The chief anaerobic isolates were Gram-negative anaerobic bacilli (especially Fusobacterium nucleatum and Bacteroides melaninogenicus) and anaerobic streptococci (Peptostreptococcus) and cocci (Peptococcus). These organisms, along with microaerophilic streptococci (these belong in the genus Streptococcus but are considered with the true anaerobes since they will frequently not be recovered unless good anaerobic transport and culture techniques are used), are the most commonly encountered anaerobes in pleuropulmonary infections of the various types in which these organisms play a role.

Dr. Murray stressed the fact that Bacteroides fragilis may be found in up to 20 percent of anaerobic pleuropulmonary infections and that this may need to be considered in selecting the antimicrobial therapy to be used. He also noted that in mixed infection one need not necessarily include drugs active against each bacterial isolate. Bartlett[2] used penicillin G successfully in seven patients with mixed infections involving B. fragilis despite resistance of this organism to the agent employed. I prefer to include an agent active against B. fragilis (clindamycin or chloramphenicol) in treating seriously ill patients with suspected anaerobic pulmonary infection until I am certain that this organism is not present or until they are no longer seriously ill.

The failure of the patient presented in the conference to respond to several agents generally active against anaerobes is of interest. The presence of resistant facultative bacteria such as Staphylococcus aureus or Klebsiella pneumoniae seems unlikely as these should be recovered readily on aerobic culture. Since there was no evidence of obstructive pathology or an undrained collection of pus to account for failure of response and since the patient responded rapidly to administration of clindamycin subsequently, the most reasonable explanation is the presence of anaerobes resistant to the agents used earlier.

There is relatively little published information on activity of cephalexin against anaerobes, but unpublished data from our laboratory (D. F. Busch, V. L. Sutter, and S. M. Finegold) indicate relatively good *in vitro* activity against anaerobes susceptible to penicillin G. The patient subsequently received rifampin, along with isonicotinic acid hydrazide (INH®), for possible tuberculosis. Rifampin is very active *in vitro* against most clinically important anaerobes except Fusobacterium varium, F. mortiferum and Clostridium ramosum.[3] However, as with other types of bacteria, resistant mutants occur with significant frequency. There is essentially no clinical experience with rifampin in anaerobic infections, but one would anticipate problems with resistance if the agent was used alone (isonicotinic acid hydrazide has no activity against anaerobes).

Penicillin G was next administered, again with unsatisfactory results—despite a dosage of 10 to 12 million units per day. My own feeling is that it is not feasible to treat many or most Bacteroides fragilis infections with even very high doses of penicillin G, although, as noted in the study by Finegold and Bartlett,[2] administration of penicillin may be effective when B. fragilis is part of a mixed flora. Ten percent of strains of B. fragilis are resistant to even 500 units per ml of this agent (V. L. Sutter and S. M. Finegold, unpublished data). Occasional strains of other anaerobes (such as Bacteroides melaninogenicus and Fusobacterium varium) are also very resistant to penicillin. It should be noted that antibiotic disc susceptibility results obtained by the Kirby-Bauer technique or other techniques not specifically standardized for anaerobes (and the particular type of anaerobe being tested) may be misleading. It should also be noted that, while penicillin G is usually the drug of choice for anaerobic pulmonary infection, other penicillins are not necessarily

suitable. Methicillin, nafcillin and the isoxazolyl penicillins (oxacillin, cloxacillin and dicloxacillin) are distinctly less active than penicillin G. Cephalosporins generally have good activity against anaerobes except for Bacteroides fragilis.

The differential diagnosis of lung abscess is outlined in excellent fashion by Dr. Murray, as is the pathogenesis of the disease. Proper stress was placed on the fact that in hospital-acquired aspiration pneumonia, nosocomial pathogens such as Staphylococcus aureus and a variety of relatively resistant Gram-negative bacilli may be involved, along with anaerobes, and that therapy must be modified accordingly. This may also be true in the case of patients in nursing homes.

Some additional comments on the importance of proper specimen collection and transport in the specific diagnosis of lung abscess and other anaerobic pulmonary infections are in order. These important considerations are the responsibility of the clinician. When empyema or bacteremia complicate anaerobic pulmonary infection, they offer convenient sources of information on the specific cause of the parenchymal process. Empyema is seen in more than a third of cases. Bacteremia, on the other hand, is uncommon in anaerobic pulmonary infection and may often not include all organisms involved in the pulmonary process. Direct lung puncture is more hazardous in adults than transtracheal aspiration, samples only a very small area and provides only a very small volume of specimen. It is my feeling that it is not established that fiberoptic bronchoscopy, even with use of a nasopharyngeal airway and the covering sleeves technique, can provide a specimen free of indigenous upper respiratory tract flora (where anaerobes are prevalent). The use of an oxygen-free tube or vial is the ideal system for specimen transport. If such a tube is stoppered with butyl rubber, anaerobes will survive at least 24 hours. However, facultative forms in a specimen may begin to multiply after a time and crowd out anaerobes (or distort the quantitative relationships). Accordingly, if a delay of more than two hours is necessary before the specimen in a gassed-out tube can be cultured, the tube should be refrigerated to minimize such multiplication.

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CASE REPORTS

Refer to: Udall JA: Cardiac pacing for cardiac arrest due to hyperkalemia plus digitalis and quinidine toxicity. West J Med 124:497-500, Jun 1976

Cardiac Pacing for Cardiac Arrest Due to Hyperkalemia plus Digitalis and Quinidine Toxicity

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LIFE-THREATENING HYPERKALEMIA may develop suddenly in cases of potassium overdosage or gradually in a variety of kidney disorders, and may remain undetected until a preterminal state has been reached. It is not widely known that cardiac pacing can be employed successfully in this emergency. Recent reviews of artificial pacing[1,2] and treatment of potassium intoxication[3,4] fail to mention cardiac pacing in managing severe hyperkalemia. Indeed, this therapeutic method has been reported in only four patients to date.[5,6] Cardiac pacing for atrioventricular block and asystole caused by digitalis toxicity has been recommended[7,8] but reports of such are rare.[9] The same is true of quinidine poisoning.[10] Emergency pacing in the management of hyperkalemia in a patient with associated digitalis and quinidine toxicity is reported here. Artificial pacing proved effective at a low excitation threshold. The heart remained contractile and responsive to extrinsic stimulation after intrinsic pacemakers failed.

Report of a Case

A 58-year-old woman with rheumatic heart disease, mitral valve prosthesis, chronic cardiac insufficiency and recurrent atrial fibrillation (Figure 1 A) was admitted to hospital for elective cardioversion. Additional diagnoses included diabetes, osteoarthritis, emphysema and chronic obstructive uropathy resulting from a lacerated left ureter.

On physical examination, the patient appeared chronically ill. A II/VI apical systolic murmur, metallic third heart sound, wheezes in both lungs, tender liver, pedal edema and Heberden's nodes were noted. Mild cardiomegaly, pulmonary congestion and interstitial fibrosis were seen on x-ray studies of the chest. Laboratory studies showed the following values: serum potassium, 5.4 mEq per liter; digoxin, 1.4 ng per ml; urea nitrogen, 17 mg per 100 ml, and prothrombin activity 40 percent.

Digoxin, 0.25 mg; furosemide, 80 mg; potassium chloride, 6 grams; potassium iodide, 1.6 gram; phenformin, 100 mg; oxytriphylline, 600 mg; indomethacin, 75 mg, and quinine, 1,000 mg were administered daily and the patient's warfarin dosage was increased for optimal anticoagulation. On the second day a misunderstanding led to a one-fold increase in the quinine dose for leg cramps; on the fifth and sixth days, 900 mg and then 1,200 mg of quinidine gluconate were given in anticipation of electrical cardioversion.

Next day the patient gradually became comatose, hypotensive, anuric and then moribund without benefit from intravenous atropine and isoproterenol therapy. Blood was drawn for determination of quinidine, digoxin, electrolyte and urea nitrogen levels. Findings on electrocardiograms (Figure 1 B-G) deteriorated throughout the day to a "sine wave" pattern which persisted for approximately an hour before a transvenous pacing electrode was inserted. Effective ventricular pacing was achieved immediately at a threshold of 0.5 milliampere (Figure 1 H). The blood pressure rose quickly to 110/70 mm of mercury, the patient became responsive within 30 minutes and a normal urine output resumed. An hour after pacing, a serum potassium level of 8.5 mEq per liter and urea nitrogen level of 36 mg per 100 ml were reported and the patient was treated with calcium chloride, 4 grams; sodium bicarbonate, 80 mEq; glucose, 50 grams, and insulin, 25 units given intravenously plus sodium polystyrene sulfonate (Kayexelate®), 100 grams given by retention enema. The electrocardiogram improved pro-

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gressively throughout the night with the pacemaker switched off at intervals (Figure 1 I-K); the patient recovered uneventfully, electrical cardioversion was carried out before discharge (Figure 1 L) and she remains alive two years later. The serum digoxin level was 3.4 ng per ml and the quinidine level 8.3 mg per liter at the height of cardiac dysfunction. Creatinine clearance measured six weeks after discharge was 26 ml per minute.

Discussion

A diagnostic puzzle confronted the staff the day this patient almost died. There was little to suggest potassium intoxication by the clinical presentation and initial tests of serum potassium and blood urea nitrogen. Tall sharp T waves commonly associated with mild hyperkalemia electrocardiographically were never seen. Characteristic tall, narrow and pointed T waves may be present, however, in only a fourth of patients with hyperkalemia.[1] With progressive bradycardia and widening of QRS complexes, it was realized the patient had received sizable doses of quinidine and quinine concurrently and an additive effect of these drugs was appreciated. Thus at the time of emergency cardiac pacing, quinine-quinidine* toxicity was the presumptive diagnosis. Hyperkalemia was not discovered and treated chemically until an hour after successful pacing had been achieved and the patient's condition had improved to a pronounced degree.

In retrospect, hyperkalemia was probably the dominant toxic factor resulting from overly-zealous potassium chloride supplementation and potassium iodide therapy in the presence of impaired renal function and from decreased renal plasma flow associated with heart failure and diuretic-induced hypovolemia. Surawicz and associates[12] reported a similar but fatal case of hyperkalemia in an elderly patient in whom heart failure was treated with sodium meralluride and 6 grams of potassium chloride daily for five days in the hospital. Indeed, the same renal and prerenal circula-

*The quinidine assay performed by Bio-Science Laboratories, Van Nuys, California is not specific, detects quinine, and the two are summated in the final quantitative result.

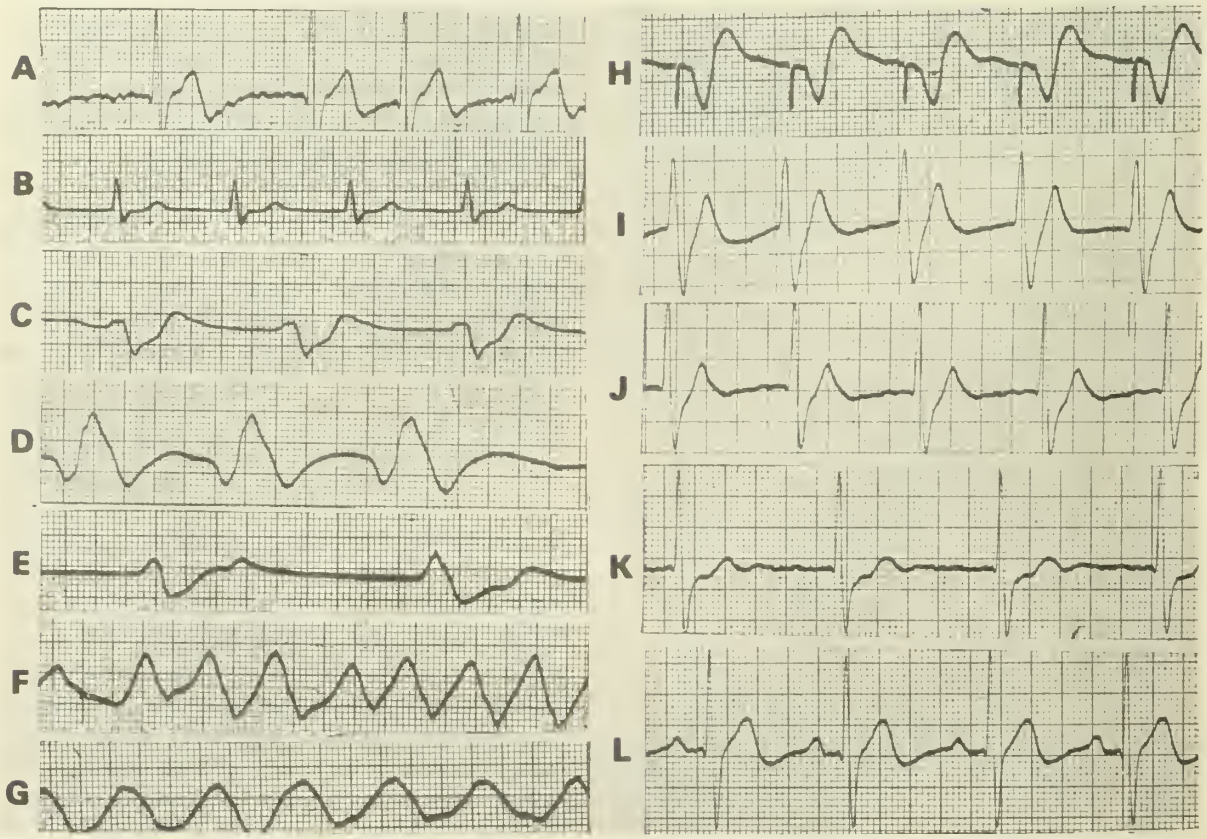

Figure 1.—The electrocardiographic sequence of cardiac arrest, artificial pacing and recovery from hyperkalemia, digitalis and quinidine toxicity. **A**, atrial fibrillation. **B**, sinoventricular or accelerated junctional (nodal) rhythm. **C, D, E**, sinoventricular or idioventricular rhythm. **F, G**, dying heart pattern. **H**, ventricular pacing. **I, J, K**, sinoventricular or accelerated junctional (nodal) rhythm. **L**, sinus rhythm.

tory disorders contributing to hyperkalemia probably led to an accumulation of quinine-quinidine and digoxin to plasma levels associated with toxicity at the time of circulatory collapse. It is well known that digoxin[13] and quinidine[14] reach higher plasma levels in patients with advanced heart disease and renal insufficiency compared with healthy subjects given comparable doses. Serum levels of digoxin in excess of 2 ng per ml[15] and quinidine in excess of 8 mg per liter[16] are commonly associated with toxicity.

Acute electro-mechanical heart failure was probably caused by a summation of potassium, quinine-quinidine and digitalis intoxication. First, the profound depression of cardiac automaticity and contractility was disproportionate to the moderate hyperkalemia measured (8.5 mEq per liter). Ventricular asytole is usually associated with plasma potassium levels above 12 mEq per liter. The extensive experience of Surawicz and associates with potassium infusions to control arrhythmias in man indicate that plasma potassium concentrations may be raised to 7 or 8 mEq per liter, temporarily at least, with no significant risk of cardiac arrest.[12] In the canine studies of Lee and co-workers[17] and Ham and co-workers,[18] ventricular stimulation thresholds have been shown to *decrease* with rising potassium concentrations up to 6.7 to 8.5 mEq per liter. Further elevations were associated with increasing excitation thresholds. Second, manifestations of quinidine toxicity include central nervous system disturbances,[10] depression of heart rate and contractility and progressive QRS widening[19] not unlike those changes observed in the patient reported here. Third, sinoatrial arrest and cardiac standstill may result from digitalis toxicity. At least one such case has been treated successfully by artificial pacing.[9] Complex interrelations exist between potassium, digitalis and quinidine, especially in patients with impaired renal function.[20,21] Digitalis may elevate plasma potassium levels in humans and provoke hyperkalemia, according to Mason and associates.[8] Decreased cardiac membrane potentials and speed of contraction induced by quinidine are accentuated by hyperkalemia[20] and the additive effects of hyperkalemia and quinidine therapy may depress myocardial contractility and result in serious toxicity.[21] Therefore, a combination of hyperkalemia, quinidine and digitalis toxicity provides the best explanation for the severity of the arrhythmias and circulatory failure in this patient when serum concentrations of potassium, quinidine and digoxin were elevated only moderately into the toxic range.

A low pacing threshold of 0.5 milliampere at the height of cardiac dysfunction was unexpected. Furman and associates[5,6] did not provide excitation thresholds in their reports of four hyperkalemic patients treated successfully by cardiac pacing. A fatal case described by Surawicz and associates[12] was refractory to pacing during an hour of cardiac arrest, then responded after treatment with adrenalin and sodium bicarbonate. The preterminal threshold was not reported. Subsequently these investigators observed increased pacing thresholds in six dogs and one human volunteer during intravenous infusions of potassium, 4- to 12-fold above preinfusion levels, but in no instance did they exceed 6 volts. Of greater interest, a top plasma potassium level above which pacing was ineffective was never reached. Potassium concentrations rose to 12, 13 and 15 mEq per liter in three dogs at which time pacing thresholds equalled only 2.9, 4.6 and 4.2 volts, respectively.

The hyperkalemic range within which life-threatening arrhythmias may occur and pacing refractoriness develops may be rather wide. The experiments of Surawicz and his co-workers[12] and the results obtained in the present case invite the exploration of the range of pacing thresholds at various levels of hyperkalemia in which the heart fails to contact spontaneously but remains responsive to artificial stimulation.

Summary

This report describes a 58-year-old woman with advanced rheumatic heart disease in whom profound electro-mechanical heart failure was treated successfully by emergency pacing. The cause for the near-fatal complication was obscure at the time of artificial pacing but hyperkalemia combined with digitalis and quinidine toxicity emerged as the cause from laboratory tests and a review of treatment and clinical course. Pacing proved effective at a low excitation threshold and the heart remained contractile and responsive after intrinsic pacemakers had failed. It is not widely known that cardiac pacing can be employed successfully in such an emergency.

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Bronchiolo-Alveolar Carcinoma Presenting as Pericardial Effusion with Tamponade

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We wish to draw attention to several occurrences of large, life-threatening pericardial effusion which have turned out to be the first major clinical manifestation of unsuspected or undiagnosed lung cancer, particularly the type referred to as bronchiolar adenocarcinoma. Three case summaries, with autopsy findings, are presented.*

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Reports of Cases

Case 1. A 55-year-old Caucasian man, a smoker, presented with a six-week history of exertional dyspnea, worsening of a chronic cough and increase in severity of chronic intermittent back and chest pain. On admission he was noted to become dyspneic on walking more than a few steps. The patient was in moderate distress with dyspnea, cough, back and lower chest pain. The neck veins were engorged. An increased anteroposterior chest diameter was noted as were a prolonged expiratory phase and diffuse rhonchi. The working diagnosis was chronic obstructive pulmonary disease with acute exacerbation of chronic bronchitis and severe myalgia secondary to cough.

Cardiomegaly and left upper and lower lobe infiltrates were seen on x-rays of the chest. On the seventh hospital day, tachycardia, tachypnea, cyanosis and pallor developed. The systolic pressure dropped to a pronounced degree, with a narrow pulse pressure. Shortly thereafter the patient died. Clinical impression of the cause of death was pneumonia due to chronic obstructive pulmonary disease.

At autopsy pleural fluid was noted bilaterally. The right lung weighed approximately 1,000 grams and there was a deep stellate central retraction on the anterior surface of the upper lobe. Microscopic sections through this area showed partially papillary adenocarcinoma, consistent with bronchiolar type, lining and permeating the crevices of an old hyalinized, partially-cavitated scar and extending into adjacent alveoli. The

pericardium was distended and the heart was surrounded by approximately 500 ml of fluid. Roughened patchy excrescences up to 2 cm in diameter were scattered over the epicardium. Viewed microscopically these areas were seen to be composed of secondary adenocarcinoma. The coronary arteries and myocardium were normal. Final cause of death was congestive heart failure due to pericardial carcinomatosis with effusion and chronic tamponade, due to metastatic bronchiolar carcinoma.

CASE 2. A 57-year-old Caucasian woman had complaint of nausea, vomiting and ankle swelling. She had recently been discharged following a stay in hospital for left lower lobe pneumonia and recurrent hepatitis. X-ray films of the chest made at that time showed left middle and lower lobe infiltrates. A diagnosis of healing pneumonitis was made and the patient was treated with supportive care without significant improvement. Several days later a rapid thready pulse, diaphoresis and venous distention developed. Systolic blood pressure dropped to 60 mm of mercury and the heart tones were weak. On electrocardiograms, nonspecific changes and a decrease in QRS voltage compared with earlier tracings were seen. Shortly thereafter the patient died. Clinical impression of cause of death was myocardial infarction or possible pericardial effusion, or both. Significant autopsy findings were limited to the thorax. On the left upper lobe of the lung there was "an area of firmness with yellow-tan cut surface." Each pleural space contained about 800 ml of serosanguinous fluid. The pericardium was notably distended and contained 1,000 ml of grossly bloody fluid. The epicardium was studded with tumor nodules up to 1 cm in diameter which were shown microscopically to consist of poorly-differentiated adenocarcinoma. There was no evidence of myocardial infarction.

On microscopic examination of the lungs, bilateral permeation of interstitial tissues, bronchial walls, lymphatics and other vessels by adenocarcinoma consistent with bronchiolo-alveolar type was noted. Final cause of death was cardiac tamponade, due to pericardial effusion from pericardial metastasis of bronchiolar carcinoma.

CASE 3. A 33-year-old Caucasian man, a smoker, presented with cough, nausea, vomiting and epigastric pain. He had recently recovered from an upper respiratory infection with associated 15 pound weight loss. He was dyspneic and had right upper quadrant tenderness and guarding. The liver was enlarged. On an x-ray film of the chest, cardiomegaly, a prominent right hilar shadow with surrounding infiltration suggestive of pneumonia, and a soft tissue hilar node were noted.

Increased dyspnea, cyanosis and distended neck veins developed, as well as rales and a paradoxical pulse. Dramatic symptomatic improvement was noted following the removal of approximately 200 ml of pericardial fluid. Findings on tests of the fluid showed adenocarcinoma, as did findings on biopsy of an axillary node. Before this, tumor had not been suspected.

Radiation therapy was begun in an attempt to prevent recurrent effusion. The patient remained quite comfortable for a few days until he died in a chair by his bed.

Grossly recognized tumor was found only in the left hilar area. The pericardial sac was thickened and distended with 800 ml of fluid. Microscopic sections of lung showed carcinoma permeating the perivascular lymphatic channels, and extending into several bronchi. A specific site of origin could not be identified, but the tumor was considered morphologically consistent with bronchiolar carcinoma. Thickened areas in the pericardium proved to consist of poorly-differentiated epithelial tumor suggestive of glandular type. Death appeared to be caused by the resulting effusion and cardiac tamponade.

Discussion

In a search for pertinent titles in recent English literature, we have been able to find only one previously-reported case of bronchiolar carcinoma in which pericardial effusion appeared and was recognized as the first major clinical event.[1] In this instance a 33-year-old Caucasian woman presented with dyspnea. Pericardiocentesis was carried out twice, with the cells proving to be normal. Because of a second recurrence of effusion, a pericardectomy was done; microscopic examination showed a poorly-differentiated tumor. At autopsy adenocarcinoma was found growing in and around an old right upper lobe lung scar. The patient died after a total illness of only six months.

All three of our patients presented with cough or had a recent history of cough. Clinical course was as short as two months and possibly as long as ten months. In each case, laboratory findings were essentially noncontributory. Two patients had dyspnea as a prominent complaint, as did the patient reported by McFadden and Dawson, while

two patients also had prominent gastrointestinal complaints, probably due to visceral congestion. In all three patients there seemed to be a sudden worsening in clinical course at some time during the stay in hospital, and tachycardia, tachypnea, venous distention and decreased blood pressure occurred. In our third case a correct diagnosis of effusion was made and the patient survived comfortably for several days following removal of pericardial fluid. Similar improvement also occurred in the quoted case. In the second patient the tentative preautopsy suggestion of possible effusion was made only after death, while in Case 1 the presence of pericardial effusion came apparently as a surprise. While two of our patients were in their middle to late 50's, one was only 33, the same age as in the quoted case. Both the younger patients related a history of upper respiratory infection about two months before onset of the symptoms for which they sought aid.

The tumor in Case 1 appears to be a representative of so-called "scar cancer." Such lesions are now recognized as a distinct entity.[1] Much has been written about possible causes of scarring and theories of induction of tumor in these scars, but the clinical presentation and course of these tumors have seldom been described.[1] The frequency of scar cancers has been estimated to be as high as 25 percent of all lung carcinoma.[1] At least half of bronchiolo-alveolar carcinomas occur in relation to scars of the lung.[2] The histology of these tumors is typically mucin-producing adenocarcinoma, but other varieties occur.[3]

Many differences of opinion exist about certain facets of bronchiolo-alveolar carcinoma. Even its very existence as a separate entity has been questioned by some. Much interest in this tumor has been generated by the uncertainty of its precise cell of origin. Of great interest to us is the fact that in our cases this poorly-defined, peculiar, glandular, papillary tumor—with tendency toward air-passage embolization and endobronchial spread as well as preservation of alveolar walls—seemed to have a propensity for spreading to the pericardium, and for presenting initially with massive pericardial effusion and tamponade.

The incidence of metastatic disease to the heart or pericardium from all primaries has been reported most commonly as around 10 percent, although rates varying between 6 and 21 percent have been quoted.[4] Such metastases originate most commonly from lung and breast, accounting for 48 percent of metastatic disease to the heart in one series.[4] Onuigbo[5] reported 27 percent pericardial involvement in 100 consecutive autopsies of lung carcinoma. Other investigators have found as high as 31 percent involvement of heart or pericardium.[6] Scott and Garvin[7] found heart or pericardial involvement in about a third of all lung and breast carcinomas. Such invasion is generally asymptomatic, or at least is overshadowed by concurrent tumor effects elsewhere.[6] Suspicion of neoplastic pericardial effusion may be worthwhile in known lung cancer patients in whom otherwise unexplained evidence of congestive heart failure develops.

However, the point illustrated in the instances reported here is that when the classical signs of tamponade are absent, or obscured in the company of the usual cardiac disabilities expected in persistent and obstructive lung disease, and the neoplasm in the lung has the often indistinct radiological character so possible in bronchiolar-alveolar carcinoma, not only the presence of pericardial effusion but the tumor process itself may be unsuspected.

Accordingly, we have regarded these experiences as an indication for an increased level of sensitivity to clues suggesting tamponade, such as paradoxical pulse, quick, distant heart sounds, pronounced venous engorgement and, possibly, confirmatory echocardiographic findings. Also indicated may be higher index of suspicion of lung carcinoma, particularly a poorly defined or undetectable bronchiolo-alveolar type, as the underlying cause.

Summary

Several instances of fatal or life-threatening pericardial effusion, presenting clinically without known cause, have been shown by biopsy or autopsy to result from unsuspected lung cancer with pericardial metastasis. The tumor is typically a bronchiolar adenocarcinoma, without obvious distinctive radiological features.

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Erythema Chronicum Migrans

A Possibly Infectious Disease Imported from Northern Europe

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WORLD TRAVEL has extended the array of diseases with which physicians are confronted. Erythema chronicum migrans (ECM)—rarely seen in the Americas although not uncommon in the Old World, primarily Northern Europe—occurred in the patient reported here three weeks after his return from an endemic area.

ECM is a large, smooth-surfaced, annular lesion with indistinct borders; the center clears while the periphery slowly expands to enormous dimensions. It is usually single, although multiple lesions have been described.[1] ECM occurs most often in exposed skin, frequently appearing weeks or months after a tick bite.[2-4] Reported associated neurologic manifestations have included headache, hallucinations, disorientation, optic atrophy, hyperesthesia, paresthesia, radicular pain (usually in an extremity involved in the lesion), vertigo, vomiting, nuchal rigidity, and in one case paresis and anesthesia of an arm having a lesion;[5] in another case, paresis of a leg following a lesion on the thigh occurred.[1] Our patient had associated cerebrospinal fluid findings consistent with lymphocytic meningitis, and presented with bilateral facial paralysis.

Report of a Case

A 46-year-old white American man had undergone right orchiectomy and radiation therapy for seminoma in July 1968, and had been under treatment for hypothyroidism for 15 years. He left the United States on June 19, 1974, and traveled through France, Belgium, Denmark and Germany, frequently taking country walks and attending several picnics in the countryside. On July 1, he was seen in an emergency room in Germany because of headache accompanied by pain in the cervicothoracic spine, was advised to return to this country, and arrived on July 10. On July 14, paresthesia developed in the right side of the tongue, followed on July 15 by the onset of right facial palsy without sensory deficit, associated with a hot, mildly tender sensation around the neck. In the emergency room of another hospital, x-ray examination and lumbar puncture were carried out. On July 20, he noted sudden weakness of the left side of the face, and was admitted to Kaiser Foundation Hospital, San Francisco. He had taken no medicine other than propoxyphene hydrochloride, 65 mg occasionally for pain, and 0.4 mg of levothyroxine daily.

Figure 1.—The large annular lesion of erythema chronicum migrans in the patient presented.

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The only abnormalities observed were a smooth, nonscaly, erythematous skin lesion 22 cm in diameter, with central clearing and indistinct edges, extending over the posterior aspect of the chest in the midline (Figure 1), its horizontal axis over the fourth thoracic vertebra. There was no tenderness along the vertebrae. Abnormal neurologic findings were weak, though present, corneal reflexes; facial diplegia, and bilateral loss of taste on the anterior two thirds of the tongue.

Hematocrit reading was 48 percent; leukocyte count, 5,800 per cu mm with a normal differential. The erythrocyte sedimentation rate (Westergren) was 24 mm per hour. Serum chemical analyses, serum protein electrophoresis, blood sugar, triiodothyronine uptake and radioimmunoassay of thyroxine showed no abnormality. Studies for rickettsiae at the Viral and Rickettsial Disease Laboratory of the State of California Department of Health showed no complement fixation titer for the spotted fever group or Q fever at dilutions less than 1:8. Response to testing for the typhus group was positive at 1:8—a finding of uncertain significance which may represent a nonspecific rickettsial antibody titer. Further studies of this specimen at the Center for Disease Control, Atlanta, Georgia, confirmed this finding but identification of a specific agent was not possible. During the acute phase, the blood showed titers of varicella and mumps viruses at 1:8; of herpes simplex at 1:64; of St. Louis encephalitis virus at 1:16. The convalescent serum showed no change in these titers, and no titer for Venezuelan or Western equine encephalitis virus. The St. Louis encephalitis viral titers may have significance in that they may reflect either earlier infection by that agent, a nonspecific elevation due to previous immunizations or cross-reacting antibodies to other Group B arboviruses, such as the tickborne group, endemic in Europe. These sera were sent to the Center for Disease Control, Ft. Collins, Colorado, where more specific arbovirus antigens are available. Hemagglutination-inhibition and complement fixation antibodies to various Group B arboviruses (Denge-2, West Nile, yellow fever, Kyasanur forest disease, Russian spring summer encephalitis, Langat, Zika, looping ill, Central European encephalitis) were elevated, and no change in titers of convalescent sera were found. The more specific neutralization tests were abandoned for technical reasons. Response to the Venereal Disease Research Laboratories (VDRL) test was negative. There was no evidence of antinuclear antibody, and C3 and C4 complement levels were normal. Findings on urinalysis were normal; appropriate studies showed no chorionic gonadotropin.

The cerebrospinal fluid was first studied July 15, at another hospital. It contained, per cu mm, 123 mg of protein (prealbumin, 1 percent; albumin, 66 percent; α_1-globulin, 5.9 percent; α_2-globulin, 8 percent; β-globulin, 9.1 percent; γ-globulin, 9.8 percent), and 56 leukocytes, all lymphocytes. On July 24, the cerebrospinal fluid contained 55 mg of protein per cu mm with an essentially normal electrophoretic pattern save for a slight increase in the percentage of albumin; 55 mg of glucose, 30 leukocytes, 99 percent lymphocytes, and showed no organisms on preparations with India ink, Gram's stain or acid-fast stain. No organisms grew on cultures, either routine or for fungus or acid-fast organisms. Response of the cerebrospinal fluid to VDRL test was negative; cytologic study showed no neoplastic cells.

No pertinent abnormalities were shown by x-ray studies of the chest or of the cervical and thoracic vertebrae; by electroencephalogram or brain scan. Findings on biopsy of the skin from the erythematous area showed one acantholytic epidermal vesicle and minor perivascular lymphocytic infiltration in the dermis, consistent with ECM. No spirochetoid bodies were noted in the skin biopsy specimen. No organisms grew on culture of the skin for aerobic and anaerobic bacteria and fungi.

During the patient's first five days in the hospital, the peripheral margins of the skin lesion expanded notably while its center cleared. On the fifth hospital day, the oral administration of 400,000 units of penicillin VK four times daily was begun. On the ninth hospital day the erythema was clearing, the facial diplegia was unchanged and the patient was discharged. One week later, the rash had cleared but the facial diplegia was unchanged. Findings on an electromyogram were consistent with bilateral nuclear or infranuclear seventh cranial nerve palsy. The patient subsequently has recovered 90 percent function of both facial nerves.

Comment

The cause of ECM has not been elucidated. Because there is evidence that it responds to antibiotics,[4,6-8] an infectious origin has been sought. Spirochetoid bodies have reportedly been found

in the skin at biopsy,[9] and positive responses to serologic tests for species of rickettsiae have been seen.[7,10] Viral causation was suggested because ECM has been associated with a meningoencephalitis similar to other tick-bite meningoencephalitides of viral origin.[2] In 1930, Hellerström[11] reported a case of ECM associated with lymphocytic meningitis, an association subsequently noted by others.[3,8,12-15] Toxic or allergic causes have been considered.[13]

The reason for central nervous system involvement is also in question. Response of these manifestations to antibiotic therapy has been reported,[3,6] but resolution of the cerebrospinal fluid abnormalities was less convincing. Thus, the concurrence of ECM and meningoencephalitis may be coincidental rather than evidence of a common cause. This was the conclusion of Putkonen and co-workers,[2] who on clinical and epidemiologic grounds inferred that the rash and the encephalitis occur coincidentally because both are transmitted by a tick, and tick-borne meningoencephalitis is endemic in Europe. In our patient there was a high stable titer to Group B arbovirus, but we were unable to discern a temporal relation between this finding and the clinical problem, or to find a specific agent responsible for the elevated titer.

The diagnosis of ECM is primarily clinical, depending on a history of exposure, the appearance of the lesion and possibly its response to antibiotics. Appearances on skin biopsy are nonspecific, and the finding of spirochetoid bodies inconsistent,[9] as are those on serologic studies for rickettsiae.[7,10] Some workers have injected extracts of the tick Ixodes reduvius into the skin and observed that the characteristic lesion was induced in patients with ECM but not in normal volunteers[3]—a test that is neither practical nor standardized. Like 50 percent or more of patients with the disease,[3,4] our patient had no history of tick bite; but he had been amply exposed, and the period that had elapsed between exposure and the initial manifestations of disease were appropriate to incubation time. Further, the lesion appeared to respond to penicillin, although spontaneous regression cannot be ruled out.

Drug sensitivity, internal neoplastic activity and fungal infection were considered as possible causes. The patient had used propoxyphene minimally, and had taken it from time to time over months before the lesion developed. We found no report of the association of ECM with propoxyphene ingestion. Neoplasia was unlikely in this otherwise healthy man who had survived removal of the seminoma longer than five years without evidence of recurrence; attempts to find metastatic tumor proved futile. The clinical course and negative cultures made a fungal origin unlikely.

The patient also had lymphocytic meningitis, perhaps unrelated to the skin lesion. A lymphocytic reaction in the cerebrospinal fluid has been known to be associated with bilateral facial paralysis; however, the temporal coincidence of the cutaneous and neurologic aspects of our patient's illness suggest that they were related. Focal neurologic abnormalities in ECM have been noted previously only in extremities that were the site of the cutaneous lesion.[1,5] We are not aware of reports of cranial nerve involvement.

Summary

Erythema chronicum migrans, seen rarely in the New World, occurred in an American who had visited rural Northern Europe. Although many cases have followed tick bite, the cause of the disease is unknown. It has frequently been accompanied by neurologic manifestations. The patient reported here presented with bilateral facial paralysis and cerebrospinal fluid evidence of lymphocytic meningitis.

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Phytobezoar and Obstruction of the Small Intestine Following Gastrectomy

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BEZOARS HAVE LONG BEEN a source of gastrointestinal problems, yet their clinical presentation has changed over the last 40 years. Classically, bezoars were first described as a cause of gastric bleeding, ulceration, perforation and peritonitis,[4] but intestinal obstruction was not a frequent occurrence. However, since 1961, when Norberg first reported obstruction of the small intestine by a bezoar in a patient in whom gastric surgical operation had been carried out, more and more cases have appeared.[7] The cause, pathogenesis and treatment of these patients have also changed. Our experience is representative of this more recently appreciated entity of obstruction of the small intestine from ingested plant matter in patients in whom gastric surgical procedures have been done.

Reports of Cases

CASE 1. In a 47-year-old woman subtotal gastrectomy with a retrocolic, Billroth II type anastamosis had been done 14 years before admission for gastric outlet obstruction secondary to peptic ulcer disease. Two years before admission she was treated for complete obstruction of the afferent loop by jejunojejunostomy. In March 1975, she was admitted to Sutter Memorial Hospital with complaints of crampy pain in the left lower quadrant of the abdomen, nausea, and vomiting of three days' duration.

On physical examination, a vague abdominal mass just to the left of the umbilicus was noted. The abdomen was tender to direct palpation, without rebound tenderness. Bowel sounds were normal. On roentgenogram of the abdomen, dilated loops of small intestine were seen with air fluid levels compatible with obstruction of the small intestine.

At operation, a 2 by 6 cm mass was found lodged in the midportion of the ileum. Proximal to the obstruction the small intestine was distended, and distally it was collapsed. The mass was removed through an enterotomy, and results of pathologic examination showed the presence of coconut fibers. Postoperatively, the patient said that she had eaten a piece of coconut cake three days before admission. The patient had an uneventful postoperative course and left the hospital seven days after operation.

CASE 2. Four years before the present admission to hospital, subtotal gastrectomy with Billroth I anastamosis for bleeding gastric ulcers had been carried out in a 63-year-old woman. A year later, gastroenterostomy was done for gastric outlet obstruction. In June 1973, the patient was admitted to Sutter Memorial Hospital with a 24-hour history of colicky abdominal pain, nausea and vomiting. Physical findings were confined to the abdomen which was tender to direct palpation on the left side. Bowel sounds were high pitched. No unusual abdominal masses were noted on palpation. On a roentgenogram of the abdomen, dilated loops of small intestine were seen compatible with obstruction.

At operation, a 4 by 6 cm mass was found in the ileum with distended small intestine proximal to the obstruction, and collapsed small intestine distal to the obstruction. The mass was removed via an enterotomy, and results of pathologic examination showed orange fibers and seeds. Postoperatively, the patient remembered having eaten half an orange on the day before admission. The patient left the hospital six days postoperatively after an uneventful recovery.

Comment

Bezoars and their associated complications have been known for many years. The term bezoars derived from the Persian, *padzahr,* (pad —protecting against and zahr—poison or counter poison); their therapeutic uses were first credited

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to Aramzoar, a 12th century Arabian surgeon.[1] Bezoars were found in the stomachs of antelopes and goats and were highly prized for their magical healing powers.[2] They were used during the Middle Ages to treat fever, skin disease, old age, dysentery, epilepsy, snake poisoning, leprosy and sexual inadequacy. However, no mention has been made of the route of administration or dosage. The 18th century British pharmacopeia retained them as a therapeutic modality, "oriental bezoars being more esteemed than domestic."[1]

Bezoars are divided into three groups. Trichobezoars are formed from hair and before modern gastric surgical procedures accounted for 55 percent of all bezoars.[3] They are most often found in women less than 30 years of age. Phytobezoars, primarily formed of vegetable matter, accounted for 40 percent of bezoars. The remaining 5 percent were either combination, trichophytobezoars, or concretions (the latter composed of shellac, consumed presumably for its alcohol content, paraffin, tar or asphalt[2]).

In DeBakey and Ochsner's review of 303 cases culled from the world literature to 1939, the most common phytobezoars were composed of unripened persimmons.[4] The phlobatannin, shiboul, is precipitated by dilute mineral acid to form an insoluble mass which congeals with the skin and seeds, accounting in the past for 75 percent of all phytobezoars.[5] Phytobezoar causing obstruction of the small intestine after gastrectomy was first reported from Germany in 1930 by Seifert.[6] The obstructing substance was sauerkraut.[6] Since 1955 more than 150 phytobezoars have been reported following gastric operations. Of these, 90 percent have been secondary to orange fibers.[6] Norberg reported 28 cases from one hospital.[7]

Comparing McQuard's list of foods causing obstruction in 1950[8] with those collected by Buchholz[6] in 1972, several differences and similarities are obvious (Table 1). In addition to high residue, several other more exotic bezoars have been reported. Latimer described the "Surgical Chinese Restaurant Syndrome,"—Chinese noodle bezoar obstructing the ileum.[9] Townsend reported three patients with renal failure after trauma in whom bezoars formed after administration of large amounts of aluminum hydroxide (Amphogel®) and sodium polystyrene sulfate (Kayexalate®). Precipitation and operative intervention for intestinal obstruction were necessary in all three patients.[10]

TABLE 1.—*List of Foods Causing Intestinal Obstruction*

Substance	*All Phytobezoars*[5]	*Phytobezoars Causing Intestinal Obstruction in Patients after Gastric Surgical Operation*[6]
Persimmon	x	x
Peaches	x	..
Oranges	x	x
Mushrooms	x	..
Bran	x	..
Apples	x	..
Figs	x	x
Cherries	x	..
Grapes	x	..
Beans	x	..
Coconut	x	x
Potatoes	x	x
Grasshoppers	x	..
Grapefruit	..	x
Cabbage	..	x
Sauerkraut	..	x
Dandelion greens	..	x
Brussel sprouts	..	x
Macaroni	..	x
Paper[13]	..	x
Kayexalate® and Amphogel®[10]	..	x
Turkey[11]	..	x

TABLE 2.—*Incidence and Location of Phytobezoars Following Gastrectomy*

	DeBakey and Oschner[4]	*Rogers, Davis, and Harle*[1]
Age	30 years or older	16 months to 61 years, mean 60 years
Sex	80% male	Male equal to female
Time after operation	.....	4.5 months to 10 years, mean 30 months
Location	Gastric 79%, intestinal 17%, multiple 4%	Gastric 80% (33%),[6] intestinal 20% (66%)[6]
Most common composition	Persimmons 80%	Oranges 90%
Symptoms	Epigastric mass, pain, weight loss, alternating diarrhea and constipation, bleeding	Nausea and vomiting, crampy abdominal pain
Morbidity and mortality	Death, nonoperative 60%, operative 5%; obstruction 26%; ulceration 24%; perforation 7.4%; peritonitis 8.2%; initition 1%	Minimal

Numerous predisposing factors may influence bezoar formation and intestinal obstruction. Poor dentition of ill fitting dentures may be present in up to 50 percent of cases.[6] In addition, many patients do not chew their food sufficiently.[8] Peristalsis is weakest and intestinal diameter the smallest 50 to 75 cm proximal to the ileocecal valve. Gastric operation may alter antral milling or allow passage of abnormally large food boluses into the small intestine secondary to alteration or removal of the pylorus. Gastric acid may be reduced after vagotomy or antrectomy, or both, altering the potency of digestive enzymes.

Phytobezoars occur with equal frequency in men and women. Age varies from 16 months to 71 years (with a mean of 60 years). They have occurred from 4.5 months to 21 years (with a mean of 30 months) after gastric operation.[2,6] Location varies, with 20 to 80 percent reported to be located in the small intestine[2,6] (Table 2). Previous operations include gastrectomy (B-II, B-I), pyloroplasty, gastroenterostomy and Whipple's procedure.[2,11] Symptoms are typical of obstruction of the small intestine: nausea, vomiting, crampy abdominal pain and abdominal fullness. Findings on roentgenograms are usually unremarkable but may show the fine stippling of trapped gas. Results of barium contrast studies may show a filling defect which may float or compress.[12] Differential diagnosis includes jejunogastric intussusception, carcinoma and suture line defects.[2]

Treatment need not be immediate operation if an obstruction is not present. Chemical dissolution with papain, acetylcysteine and sodium bicarbonate may be successful. Cellulase lavage and mechanical disruption through a gastroscope using biopsy forceps were successful in three of eight patients.[2] However, with intestinal obstruction, operative intervention is the treatment of choice. The bezoars should be manually broken apart and pushed into the cecum. If it is impossible to disimpact the intestine by closed technique, then enterotomy and evacuation should be done. The entire gastrointestinal tract should be explored because of the 4 percent incidence of multiple bezoars.[4] Most efforts are aimed at prevention. Following gastric surgical procedures, a patient should be advised to chew food thoroughly and also warned of the danger of eating oranges, potatoes and other fibrous vegetables.

Phytobezoars are a significant complication of gastrointestinal operations. They are best treated by prevention; however, when signs and symptoms of intestinal obstruction are seen, aggressive surgical management is indicated and offers excellent results.

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LETTERS *to the Editor*

"Confidential" Examinations

To the Editor: *The New York Times* in late 1975 published an interview with a microbiologist who had developed and administered one of those many "confidential" voluntary assessment examinations so common in today's medical scene. The *Times* probably discovered the confidential test in an article based on the test that appeared in *The New England Journal of Medicine* (293:1291-1295, Dec 18, 1975). The interviewed expert was appalled that we American physicians didn't know beans about antibiotics. One of the results that apparently horrified the expert was the question on the alternative choice to penicillin in treating primary syphilis if the patient is penicillin sensitive. As for myself, practicing medicine full-full time, I couldn't help but chuckle. I have not seen a case of primary syphilis in five years and in all my 27 years of practice do not recall one patient with primary syphilis where an alternative to penicillin was needed. I too didn't know the answer but undoubtedly would have looked it up, as most of my other colleagues would have done. Subsequently during the week of January 26 to January 30, 1976 *The New York Times* ran a five-part, front-page series on incompetent American doctors, citing the interview with the antibiotic expert and his test.

Without belaboring the point, without going into that reflex defensiveness we are all getting to develop so well for all social gatherings, without showing anger for the full-time academic community and their politician supporters, the only reasonable conclusion I have reached is to send out a clarion call to all clinicians: Do not trust the word "confidential" and do not take any exam, no matter how much fun it may seem to be, unless the exam was developed by an organization you have come to trust and know in your heart of hearts has your interest and only your interest in mind. (And that principle should apply to state medical boards that send out survey questionnaires about your race and other matters.)

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Physician Extenders Opposed

To the Editor: Volume 124, March 1976, contains two articles on "The Health Care Team" [Glenn JK, Goldman J: Strategies for productivity with physician extenders, pages 249-257; Oseran LS: Physician's assistants in California, pages 258-263], neither of which was written by a physician, and an editorial [On extending patient care with physician extenders, page 234] on the same topic which was.

It is my opinion that our sociologists and social planners are running an experiment on the entire community and are currently endeavoring, as a prelude to the "inevitable National Health Insurance" to devise a means of decreasing the overall cost of medical care for our community without concern for quality.

The most obvious approach they have taken has been the development of the Medex, Nurse Practitioner, P.A. [Physician's Assistant], etc. They seem to be less concerned with the quality of care delivered than with the fact that they will, in fact, deliver care. I find it difficult to accept the fact that the nonphysician should be charged with performing medical tasks and making decisions independently.

It appears to me that we are embarking on a two level highway; on the upper highway will be university-trained physicians who will deliver health care to the affluent and probably the politicians and on the lower level will be nurse practitioners and paramedics and/or midwives who will deliver health care to the community.

I do not feel that I can endorse the use of "barefoot physicians" or feldshers in our society. I do not feel that I should be asked to be responsible for their actions. I refuse to be responsible for their actions.

I strongly suggest that we, as physicians, evaluate these programs for what they are in fact: degradation of the practice of medicine at the expense of the public's health. We should oppose these programs and expose them for what they are, second rate medicine.

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Trauma Rounds

Chief Discussants
ROBERT FREEARK, MD
JOHN DAVIS, MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is one of a series of Conferences on Trauma at San Francisco General Hospital

Refer to: Freeark R, Davis J: Shock (Trauma Rounds). West J. Med 124:510-513, Jun 1976

Shock

EDWARD VERRIER, MD:* The case we wish to discuss today is that of a 69-year-old man who was involved in a high speed automobile accident and was admitted to San Francisco General Hospital shortly after injury.

On initial assessment in the trauma room, the patient was comatose. Blood pressure was 70/0 mm of mercury and there was pronounced peripheral vasoconstriction. An endotracheal tube was immediately placed and large bore cutdowns were established in the antecubital fossa and at the ankle. After volume resuscitation with two liters of Ringer's lactate solution, vital signs stabilized at near normal levels permitting diagnostic assessment to be carried out.

No evidence of external head trauma was found but there was extensive bleeding from a facial laceration below the right eye. The pupils were bilaterally fixed with minimal light response. On examination of the chest, rib fractures were palpable on the right; however, breath sounds were equal in both hemithoraces. Findings on examination of the abdomen were unremarkable, but because of lack of consciousness and evidence of body trauma, peritoneal lavage was carried out; there was a bloody return. A compound fracture of the right leg was noted to be present. Urine was clear on analysis. The hematocrit reading was 35 percent.

On x-ray films no skull fracture was seen; however, anterior dislocation of the C-1 cervical spine was noted. Fractures of ribs 7 and 8 on the right were confirmed by x-ray studies of the chest. Findings on an intravenous pyelogram showed good excretion bilaterally. A cystogram was not done. On x-ray films of the long bones, a right tibial-fibular fracture was seen. During x-ray examination, the patient's blood pressure again dropped and he was taken immediately to the operating room. Administration of prophylactic antibiotics was begun shortly following induction of anesthesia.

On exploratory laparotomy, two units of whole blood—from a ruptured spleen—was present in the peritoneal cavity. Splenectomy was carried out. Concomitantly, facial fractures were reduced and bleeding from maxillofacial injuries controlled. Despite administration of six units of blood, hypotension occurred once again. Tube thoracostomy was done and 600 ml of whole blood was noted in the right side of the chest. After this, bilateral exploratory burr holes were carried out and brain contusion was shown to be present, but no epidural or subdural hematoma. The compound right leg fracture was debrided and stabilized in plaster. A total of 17 units of whole blood was required by the time surgical procedures were completed.

The postoperative course was stormy, charac-

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terized by coma for the first four days. This cleared somewhat over the next week and seemed to respond to steroid administration. Another major problem was respiratory insufficiency. Positive pressure ventilation and 40 percent oxygen were required initially to maintain the patient's arterial partial pressure of oxygen (Po_2) at 60. This deteriorated on day five as manifested by increasing pulmonary infiltrates and deteriorating pulmonary function despite positive end expiratory pressure (PEEP). Pseudomonas was cultured from the trachea. Despite treatment with gentamycin, progressive pulmonary deterioration occurred. Overt sepsis developed, with positive blood cultures and a fall in peripheral perfusion and urinary output. Despite optimal fluid replacement and ionotropic cardiac support the patient died on the eighth postoperative day.

DONALD TRUNKEY, MD:* *This case represents all the problems manifested by a patient resuscitated from major injury and advanced shock. We are privileged today to have Dr. Robert Freeark who is Professor and Chairman of the Department of Surgery at Loyola University and Dr. John Davis who is Professor and Chairman of Surgery at the University of Vermont to discuss this particular case. I would like to ask Dr. Freeark to open the discussion and ask him to direct his remarks to hypovolemic shock.*

ROBERT FREEARK, MD:† This patient initially exemplified the most common cause of shock in trauma patients, a reduction of circulating volume. Although in this patient there were multiple sources of bleeding we must remember that there are other sources of volume loss in severe shock. The principal of these is sequestration of fluid in the intracellular space. Third space loss into bowel and body cavities contributes to the hypovolemic state. Therefore, the first thing that must be done in resuscitation of hypovolemic shock is volume replacement.

One must be aware, however, of other possible causes of shock in trauma patients—particularly those causes related to the heart, such as myocardial contusion or tamponade. Another possibility is tension pneumothorax from a combination of lung laceration and positive pressure ventilation. These are associated with high central venous pressures, as opposed to shock due to hypovolemia. Therefore, it is imperative to look at the neck veins. If they are full or a central venous pressure measurement is high, the cause of shock is cardiogenic or pulmonary.

With these few exceptions, after the described venous assessment one can assume that most shock in the trauma patient is hypovolemic. Immediate fluid replacement should be begun by placing large-bore cutdowns and starting infusion of Ringer's lactate solution. At the same time, a specimen of blood should be sent for cross matching and an ample supply of blood obtained. We infuse the first two to three bottles of Ringer's lactate solution just as fast as possible—that is, within 5 to 10 minutes. The sodium load is of no consequence as long as the patient is in shock. Adequate resuscitation is determined by a good urine output from a bladder catheter—that is at least a ml of urine per minute in an average adult. Other useful signs include good peripheral perfusion and improvement in sensorium.

There is considerable speculation regarding the nature of organ failure following hypovolemic shock. It has been my observation that with prompt correction of volume deficits, the incidence of such problems as respiratory failure of this type results from secondary complication of sepsis which occurred in this patient.

DR. TRUNKEY: *What is the role of overhydration in respiratory distress?*

DR. FREEARK: As I indicated earlier, I believe that prompt resuscitation with Ringer's lactate solution is optimal therapy. I do not believe the fluid therapy causes the lung lesion. I agree with Dr. Blaisdell's concept that the advanced shock lesion is a lesion consisting of diffuse increase in the vascular permeability. These leaky lung vessels result in the "wet lung" seen following shock. Failure to restore adequate volume results in persistent shock aggravating the leak. Overhydration may increase lung edema but this type of edema is readily reversible, while the former is not.

F. WILLIAM BLAISDELL, MD:‡ *Dr. Freeark, in view of the subsequent outcome in this case, in which prophylactic antibiotics were administered because of compound fracture, would you comment on the use of antibiotics in hypovolemic shock?*

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DR. FREEARK: I do not know all the details in this case, but certainly respiratory distress syndrome and sepsis developed. Since the organism was pseudomonas it is safe to speculate that the use of prophylactic antibotics may have set the stage for this opportunistic infection. To my knowledge there is no evidence that the use of antibiotics, when started early, will prevent the adult respiratory distress syndrome, particularly when they are used in a shotgun or nonspecific manner. I do not have a strong opinion on the use of antibiotics, but would use them for specific clinical indications such as compound fracture or grossly contaminated wounds. I would start administration as early as possible—preferably in the Emergency Room.

DR. BLAISDELL: *What about the use of steroids in hemorrhagic shock? Do they stabilize cell membranes and prevent further problems?*

DR. FREEARK: There is no convincing evidence that the use of steroids in hypovolemic or cardiogenic shock have any salutory effect. I also think we have enough evidence now that steroids may do harm by depressing the immune mechanism. I am not even convinced that they should be used in head trauma. I believe that they probably did more harm than good in this particular instance.

DR. TRUNKEY: *Let's move on to the second problem in this case, septic shock, and ask Dr. Davis to discuss this.*

JOHN DAVIS, MD:* The patient in this case had been severely injured and there had been two instances of hypotension, one initially and one intraoperatively. This in addition to such other factors as major soft tissue injury is probably why sepsis developed and the patient died. Other contributing factors would include the endotracheal intubation, the chest injury, the multiple transfusions and the surgical operation. He may have aspirated with his initial injury. It is not unusual for pseudomonas to present as it did in this case. Pseudomonas is a saprophytic organism that causes little in the way of clinical problems until there is tissue damage or shock. Then it seems to be able to overcome host defenses and obtain a foothold. The use of prophylactic antibiotics such as the cephalosporins seems to increase its incidence relative to other organisms. With contamination of the airway, a rapidly spreading bronchopneumonia then develops and the patient's condition deteriorates over a period of 24 to 48 hours.

DR. TRUNKEY: *We certainly agree with that concept and we also feel that the steroids may play a very important role since in the injured patient there probably is an immunodeficiency that is just added to by the steroids.*

DR. DAVIS: As you know this is a controversial point and when sepsis develops we prefer to use steroids, particularly in large doses. The theoretical benefits would include a reduction of the capillary membrane leak and lysosomal breakdown and there may be an ionotropic effect on the heart. I am not sure, however, that use of steroids would have made a difference in this case, or that their clinical benefit has been established beyond question. You do occasionally see a patient, however, in whom there is response to the use of steroids, at least temporarily, and for that reason I continue to use them.

DR. BLAISDELL: *Dr. Davis, would you give us a definition of septic shock? Do you believe there is such an entity?*

DR. DAVIS: Yes, I think septic shock is a distinct entity. Most shock is hypovolemic or cardiogenic. Septic shock is decreased nutritive perfusion that may actually develop in the face of increased cardiac output, suggesting that there may be arteriovenous shunting. It is not a simple volume defect and it is not a simple pump defect. It may be a combination of both. There are certainly peripheral vascular effects secondary to sepsis that produce diffuse vascular permeability with loss of vascular volume into the interstitial tissues. There may well be certain "toxic" problems that occur because of septic invasion of tissues. These toxins are characteristic of Gram-negative infection but in some instances may also be associated with Gram-positive infections. Hypotension ultimately develops, with inadequate perfusion as manifest by lactic acidosis. Decreased peripheral perfusion develops and terminally cardiac depression occurs due to the "toxic" effects of advanced infection.

DR. BLAISDELL: *Dr. Davis, would you comment on the specific aspects of treatment of septic shock?*

DR. DAVIS: Treatment is threefold: (1) remove the source of infection, (2) correct the volume

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deficit and (3) support the heart. The first is often easier said than done, particularly in cases such as the one presented today where the problem was diffuse. Blood, urine, wound and sputum smears or cultures, or both, will define the organism and direct specific antibiotic therapy. Abscesses or other sources of infection that can be treated by surgical drainage should be looked for and treated promptly and definitively. Gallium scans now provide a means of locating intraperitoneal infections so as to permit simple direct drainage of intraperitoneal collections or pus.

Patients with sepsis require vigorous fluid therapy so as to maintain urine output. Central venous pressures or left-sided cardiac pressures should be monitored using a Swan-Ganz catheter. High pressures associated with poor perfusion should be treated with cardiotonic drugs. These may include isoproterenol (Isuprel®), dopamine or steroids depending upon your clinical experience and the response of the individual patient.

DR. BLAISDELL: *Dr. Freeark, do you have any comments to add to the concept of septic shock?*

DR. FREEARK: I would agree with Dr. Davis. I am sure that septic shock has a direct effect on the heart and would like to emphasize the importance of support of the myocardium during sepsis. I also think we have to keep in mind that when sepsis involves a large surface it may produce a severe volume deficit and large amounts of volume replacement may be required for proper resuscitation.

DR. BLAISDELL: *Dr. Davis, do you feel that severe trauma or shock depresses the immune system?*

DR. DAVIS: That is a difficult question. If one were to take a number of patients such as the one discussed today, resuscitate them and treat them in the same way, some would survive and some would die. I do not know if there is an immune defect in those that die. I think there is evidence that shock and trauma are additive and do in some way increase susceptibility to infection. In the patient discussed today there were two episodes of hypovolemic shock and both may have contributed to an immune deficiency.

FRANK LEWIS, MD:* I would like to second Dr. Freeark's recommendation against using steroids in the presence of an injury to the head. For some years the British did not use steroids following head trauma, believing them to be of no value. It has been my impression working in the intensive care unit that in patients with head injury and multiple trauma treated with steroids there is a special risk of their conditions suddenly deteriorating because of sepsis. In these patients standard treatment also tends to be less effective and a deterioration of condition may occur in a much shorter time than in patients not so treated.

DR. FREEARK: I would like to mention one other complication of steroid therapy: the problem of peptic ulcer. I recall a patient who died because of this complication while recovering from head injury. Because of this I have followed the literature very carefully and I can find no convincing evidence that administration of steroids is beneficial in traumatic brain injury.

DR. BLAISDELL: I would like to thank our two discussants today—Drs. Freeark and Davis. We have been honored to have them visit us. They have made a number of important points, which I will summarize. The primary treatment of hypovolemic shock is volume replacement. Volume replacement must be sufficient to correct blood volume losses and also third space loss due to vascular permeability changes, losses into the cells and sequestration of fluid in the gut and body cavities. Severe hypovolemic shock seems to render the patient vulnerable to infection probably via depression of immune defenses so that sepsis is not prevented by prophylactic antibiotics. In fact, administration of antibiotics seems, if anything, to increase the incidence of virulent infections such as pseudomonas. Septic shock results from a combination of cardiac depression and volume loss due to an increase in vascular permeability generated by toxins liberated by the infecting organisms. Nonnutritive blood flow or arteriovenous shunting aggravates the circulating deficit. Treatment consists of (1) eradicating the infection by surgical drainage or specific antibiotic therapy, (2) establishing adequate volume and (3) myocardial support.

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Information

Refer to: White LP: Biomedical experimentation on prisoners—Report of the Committee for Continuing Study of Evolving Trends in Society Affecting Life, California Medical Association (Information). West J Med 124:514-516, Jun 1976

Biomedical Experimentation on Prisoners

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SINCE EARLY 1975, the Committee on Evolving Trends in Society Affecting Life* of the California Medical Association has been examining the issues related to the ethical considerations of biomedical experimentation on prisoners. It has had available to it an abundance of information and divergent points of view as to whether such experimentation on prisoners represents a proper area of involvement for physicians and, if so, under what conditions they should participate. The Committee's inquiry was prompted by a request made simultaneously to the San Francisco Medical Society and to the California Medical Association by the medical administrator of the Prisoners' Health Project of San Francisco, who urged these organizations "to oppose *in toto* the use of prisoners as experimental subjects and to insist that the Nuremberg Code, prohibiting such use, be stringently applied." "Other countries," he asserted in his communication, "have demonstrated that they are able to carry out necessary research involving human subjects without resorting to the prison population. We can and must do likewise."

The literature surrounding the subject of biomedical experimentation on prisoners is voluminous. This matter has received worldwide attention and has been the focus of conferences and international legal proceedings, particularly following World War II. The array of books, reports and articles to which the Committee has referred contains sufficient supportive information on which we feel our recommendations can be made and to which any person interested in probing the subject can refer at greater length (see bibliography). A number of people, familiar with various aspects of the subject, and to whom the Committee expresses its appreciation, assisted in the deliberations. For the purpose of this report, the Committee considers it only necessary to allude to topics such as "informed consent," "the value of experiments conducted," "the construction and supervision of the research protocol," "the nature of voluntary participation" and "the experimental setting" in order to evoke discussion and stimulate debate regarding the use of prisoners for such experimentation.

Pros and Cons of Biomedical Experimentation on Prisoners

The essential arguments posed by those who favor or oppose biomedical experimentation are summarized below. No attempt has been made to evaluate their relative importance. Each summary is followed by brief amplifying comments. They have either been abstracted from the extensive literature or reflect statements made to the Committee.

Pros

1. Monetary reward:
   (a) During incarceration
   (b) For use following release
   (c) No other comparable source of income
2. Relief from boredom
3. Parole advantages
4. Advantages and conveniences (food, quarters, work assignments, medical care not otherwise available and so forth)
5. Protection from other prisoners (from violence, sexual molestation and the like)
6. Altruism
7. Peer approval
8. Opportunity for contact with outsiders (treated as "human beings")
9. Opportunity to obtain some degree of recognition
10. Contribution to medical knowledge and phar-

A Report by the CMA Committee for Continuing Study of Evolving Trends in Society Affecting Life approved by the Council of the California Medical Association, March 27, 1976.

Members of the Committee are: Laurens P. White, MD, Chairman; Roberta Fenlon, MD; James H. Ford, MD; Frank J. Glassy, MD; Herbert A. Holden, MD; Homer D. Peabody, Jr., MD; James C. Roberts, MD; Robert Stragnell, MD; Edgar Wayburn, MD; Charles Clanton, Medical Student, and Albert R. Jonsen, PhD, Consultant.

Reprint requests to: Committee for Continuing Study of Evolving Trends in Society Affecting Life, California Medical Association, 731 Market Street, San Francisco, CA 94103.

*The Committee on Evolving Trends in Society Affecting Life was established three years ago as a Committee of the House of Delegates for the purpose of exploring ethical issues of current interest to the medical profession. Among its areas of study have been abortion, euthanasia, death and dying, and rape.

maceutical advances which may decrease the cost of important drugs
11. Cohesive population enabling:
    (a) Control
    (b) Surveillance
12. Prisoners' assertion that they have a "right" to choose to participate
13. Tends to result in upgrading of medical services in the prison as a whole
14. Reported difficulty in securing other subjects

The proponents of such experimentation contend that informed consent is a prerequisite for prisoner participation and therefore they have the right to refuse to participate in, or to withdraw from, a given experiment. They assert that experiments are carefully developed and controlled in a setting where prisoners can be supervised and treated immediately for any adverse effects. The inability to use prisoners, they state, would prevent the development of new drugs and treatment. Furthermore, they aver that many prisoners participate in such experiments because it enables them to accumulate some money by the time their terms are up or to assist their dependents in some small way. That such participation in biomedical experimentation relieves the monotony and boredom of prison life and gives prisoners an opportunity to contribute their services in some meaningful manner, thereby also assisting in some aspect of the rehabilitation process, is one of the more forceful arguments used. And it is claimed that the existence of such a program can result in the upgrading of medical services in a prison as a whole.

Cons

1. Consent may be based on factors such as:
    (a) Availability of monetary rewards in contrast to prison allowance
    (b) Real or imagined parole advantages
    (c) Promise of material advantages
    (d) Avoidance of unpleasant experiences (such as violence)
    (e) Educational and cultural deprivation
2. Validity of informed consent may be difficult to ascertain or evaluate
3. Prisoners are used as objects to possible benefit of others
4. "Free choice" limited by virtue of incarceration
5. Some experiments represent:
    (a) Subsidization of pharmaceutical industry
    (b) Frequently redundant research
6. Prisoners can "beat the system" by:
    (a) Trying to determine outcome desired by investigators
    (b) Exchanging drugs with other prisoners
    (c) Not subscribing to regimens
7. Pervasive use of illicit drugs in prisons
8. Exposure to range of undesirable outcomes (reluctance to reveal side effects facilitated by closed environment)
9. Lack of medical care or disability insurance protection for prisoner or dependents, or both
10. Other populations available (Western European experience)
11. Medical facilities inadequate; prisoners who become ill are treated elsewhere in community
12. Experimentation used as manipulative device by prison authorities and other prisoners
13. Population more transient than often assumed

The opponents of such experimentation contend that inmates cannot truly give "informed consent" in view of the constraints imposed upon them by virtue of their prison status. These include the availability of monetary rewards in contrast to the meager prison allowance, their belief that parole advantages will accrue to them, favored treatment that they actually do receive as a result of their participation and avoidance of unpleasant experiences by virtue of this segregation. They maintain that the educational level of prisoners is frequently so low as to prevent them from understanding the essential nature of an investigator's research objectives. Therefore, the validity of informed consent is difficult to ascertain or to evaluate and consequently is virtually nonexistent. They also assert that investigators have been known to conceal all of the essential elements of the research protocol. Prisoners receive better food, quarters and treatment by virtue of their involvement in research—factors that influence the decision of inmates to participate. Research protocol and supervision have been reported to be inferior to the claims made for them; it is not uncommon for prisoners "to beat the system" by not following the experimental regimen or by exchanging drugs with other prisoners.

Illicit drug traffic in prison may negate the purpose of the experiment and the prisoners can tell the investigator what the latter would like to believe, as determined through the grapevine system

of the prison. The risks taken by a prisoner can be formidable, with inadequate provision for medical attention or for disability insurance protection in the event of serious or prolonged illness. It is generally acknowledged that most prisons are deficient in the provision of medical services and that when injury or illness do occur, community facilities must be used to provide care in such instances.

Although proponents of experimentation in prisons assert that the prison population is a more or less "homogeneous" one in terms of population stability, opponents maintain that the prison population is transient. Opponents aver that the United States is the only country that permits such medical experimentation on prisoners. Virtually all European countries do not approve the use of prisoners for such research purposes. It is asserted that a sufficient number of volunteers, other than prisoners, are recruited. It is also contended that prisoner experimentation represents a substantial subsidization to the pharmaceutical industry in the United States without commensurate economic benefits to the public for whom the benefits of such research are intended.

Summary Observation

The fundamental ethical issue—one that should be the primary determinant in the use of prisoners for biomedical experimentation—is whether as members of a captive group they can exercise free will or free choice or whether their freedom is so constrained that they cannot. While the proponents of such experiments acknowledge that many abuses have occurred in the past, they cite examples of how shortcomings need not exist if appropriate measures are taken. Their primary appeal is that there are potential benefits to be derived. On the other hand, the opponents base their claims on the reported recurrent abuses and on the basic ethical issue which is dominated by the prison setting.

Recommendation

Following lengthy discussions and deliberations, and consideration of several alternatives, the Committee on Evolving Trends in Society Affecting Life recommended *that biomedical experimentation on prisoners be done only when the following minimum standards and conditions are met:*

1. Existence of a first-rate medical department in the institution, available to all prisoners, adequately staffed and equipped, and *subject to outside certification* by a medical professional group.
2. Establishment of an institutional review body, with representation from prison authority, inmates and medical professionals for the purpose of:
   (a) review, evaluation and approval of proposed research, procedures and protocol to be observed, and
   (b) serving as an appeal body for prisoner complaints.
3. Creation of an outside scientific review body with representation from an institutional review body or institutional review bodies and including public members and prisoner representatives to:
   (a) assure adherency to, and compliance with, protocol, including ethical components;
   (b) safeguard legitimate interests of prisoners, experiment sponsors and investigators alike;
   (c) evaluate outcome of experiments;
   (d) serve as a grievance and appeal body for all parties concerned, and
   (e) recommend improvements in various aspects of the experiment, as determined through analysis of all components of research and experimentation, with
   (f) periodic reports made available to all parties concerned as well as to the public.
4. Assurance of medical care and disability benefits for prisoners who incur complications resulting from their participation in biomedical experiments.
5. Provision for adequate remuneration and alternative work opportunities for all prisoners at comparable rates.

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- Surgical management of primary operable carcinoma of the breast
- Radiation therapy and chemotherapy—adjuvant and palliative in management of carcinoma of the breast
- How do we tailor therapy of operable breast cancer to fit the individual patient?

in memoriam

Bednarz, Walter J., Menlo Park. Died March 26, 1976, aged 62. Graduate of the Creighton University School of Medicine, Omaha, 1939. Licensed in California in 1940. Dr. Bednarz was a member of the San Francisco Medical Society.

Bieler, Henry G., Capistrano Beach. Died October 11, 1975, aged 81. Graduate of the University of Cincinnati College of Medicine, 1916. Licensed in California in 1927. Dr. Bieler was a member of the Orange County Medical Association.

Blachman, Louis E., Beverly Hills. Died January 16, 1976 in Los Angeles of cerebral ischemia due to pulmonary edema, aged 79. Graduate of Western Reserve University School of Medicine, Cleveland, 1921. Licensed in California in 1951. Dr. Blachman was an associate member of the Los Angeles County Medical Association.

Bradburn, Ian Muir, La Jolla. Died March 25, 1976 in La Jolla, aged 50. Graduate of Tulane University School of Medicine, New Orleans, 1948. Licensed in California in 1953. Dr. Bradburn was a member of the San Diego County Medical Society.

Brown, Velva V., Berkeley. Died March 29, 1976 in Oakland of cancer of the endometrium with metastases, aged 84. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1921. Licensed in California in 1922. Dr. Brown was a retired member of the Alameda-Contra Costa Medical Association.

Carter, Martin G., Los Angeles. Died March 18, 1976 in Glendale of heart disease and carcinoma of the pancreas, aged 89. Graduate of Cooper Medical College, San Francisco, 1910. Licensed in California in 1910. Dr. Carter was a retired member of the Los Angeles County Medical Association.

Chope, Harold D., San Mateo. Died April 24, 1976 in San Mateo of heart disease, aged 72. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1931. Licensed in California in 1931. Dr. Chope was a retired member of the San Mateo County Medical Society.

Cowan, Clarence B., San Francisco. Died March 26, 1976 in San Francisco, aged 83. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1923. Licensed in California in 1923. Dr. Cowan was a retired member of the San Francisco Medical Society.

Cunningham, Ernest Lloyd, Fresno. Died March 21, 1976, aged 69. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1937. Licensed in California in 1946. Dr. Cunningham was a member of the Fresno-Madera Medical Society.

Davis, Wilhelmena Harriett, Burbank. Died December 28, 1975 of injuries received in airplane accident, aged 58. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1944. Licensed in California in 1944. MD degree from California College of Medicine, 1962. Dr. Davis was a member of the Los Angeles County Medical Association.

Ehmke, Edwin C., Los Angeles. Died March 7, 1976, aged 68. Graduate of the University of Minnesota Medical School, Minneapolis, 1935. Licensed in California in 1939. Dr. Ehmke was a member of the Los Angeles County Medical Association.

Fate, John C., Los Angeles. Died July 26, 1975 of heart disease, aged 83. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1922. Licensed in California in 1922. Dr. Fate was a member of the Los Angeles County Medical Association.

Holder, Hall Gilliam, Del Mar. Was killed April 3, 1976 in an automobile accident in Saratoga, aged 77. Graduate of Cornell University Medical College, New York, 1924. Licensed in California in 1927. Dr. Holder was a retired member of the San Diego County Medical Society.

Johnson, Henrietta May, Pasadena. Died March 19, 1976, aged 85. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1923. Licensed in California in 1932. Dr. Johnson was a member of the Los Angeles County Medical Association.

Kolisch, Peter, San Francisco. Died June 21, 1975, aged 77. Graduate of Medizinische Fakultät der Universität, Wien, 1923. Licensed in California in 1939. Dr. Kolisch was a member of the San Francisco Medical Society.

London, Milton Z., Los Angeles. Died February 10, 1976 in Los Angeles of cerebrovascular accident, aged 63. Graduate of the University of Southern California School of Medicine, Los Angeles, 1937. Licensed in California in 1937. Dr. London was a member of the Los Angeles County Medical Association.

Loomis, Richard A., Fallbrook. Died April 15, 1976 in Fallbrook of cancer, aged 57. Graduate of the University of Buffalo School of Medicine, 1943. Licensed in California in 1959. Dr. Loomis was a member of the San Diego County Medical Society.

Lucas, Wilbur, Santa Monica. Died July 17, 1975, aged 102. Graduate of Northwestern University Medical School, Chicago, 1903. Licensed in California in 1923. Dr. Lucas was a retired member of the Los Angeles County Medical Association.

Mac Eachern, Katherine Hypatia, Escondido. Died June 16, 1975, aged 66. Graduate of the University of Illinois College of Medicine, Chicago, 1936. Licensed in California in 1936. Dr. Mac Eachern was a member of the San Diego County Medical Society.

McCune, Donovan James, Vallejo. Died April 11, 1976 in Vallejo, aged 75. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1928. Licensed in California in 1951. Dr. McCune was a retired member of the Solano County Medical Society.

McDermott, Thomas Joseph, Glendale. Died February 11, 1976, aged 49. Graduate of Northwestern University Medical School, Chicago, 1954. Licensed in California in 1958. Dr. McDermott was a member of the Los Angeles County Medical Association.

McGuinness, John Edward, San Francisco. Died June 20, 1975 of pneumonia, aged 73. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1928. Licensed in California in 1928. Dr. McGuinness was a member of the San Francisco Medical Society.

McMeekin, Hugh Ralston, Palm Springs. Died March 22, 1976, aged 75. Graduate of the University of Nebraska College of Medicine, Omaha, 1925. Licensed in California in 1930. Dr. McMeekin was a member of the Los Angeles County Medical Association.

Moore, Marion O., Los Gatos. Died April 26, 1976 in Placerville of heart disease, aged 71. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1943. Licensed in California in 1943. MD degree from California College of Medicine, 1962. Dr. Moore was a retired member of the Forty First Medical Society.

Paez, Julio, San Diego. Died February 25, 1976, aged 77. Graduate of Rush Medical College, Chicago, 1924. Licensed in California in 1924. Dr. Paez was a retired member of the San Diego County Medical Society.

Sedgwick, Darrell S., Capitola. Died April 16, 1976 in Santa Cruz, aged 57. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1944. Licensed in California in 1944. Dr. Sedgwick was a member of the Santa Cruz County Medical Society.

Smith, Gene Stanley, El Cerrito. Died March 20, 1976 in El Cerrito, aged 52. Graduate of the University of Colorado School of Medicine, Denver, 1947. Licensed in California in 1951. Dr. Smith was a member of the Alameda-Contra Costa Medical Association.

Toller, Rudolph Benedict, Santa Rosa. Died July 31, 1975 of ruptured abdominal aortic aneurysm, aged 70. Graduate of Creighton University School of Medicine, Omaha, 1929. Licensed in California in 1929. Dr. Toller was a retired member of the San Joaquin County Medical Society.

Wackerli, Gladys E., Northridge. Died April 2, 1976, aged 70. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1929. Licensed in California in 1929. MD degree from California College of Medicine, 1962. Dr. Wackerli was a member of the Forty First Medical Society.

Warner, Harold W., San Diego. Died March 18, 1976, aged 67. Graduate of Wayne University College of Medicine, Detroit, 1940. Licensed in California in 1943. Dr. Warner was a member of the San Diego County Medical Society.

Yabroff, Samuel W., Oakland. Died January 18, 1976 in Napa, aged 77. Graduate of the University of California Medical School, Berkeley-San Francisco, 1931. Dr. Yabroff was a retired member of the Alameda-Contra Costa Medical Association.

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

TRADITIONAL ACUPUNCTURE FOR TODAY—Edward John Ettl, MD, FACP, Acupuncture and Pain Clinic of El Paso. Comographix, Inc., Southwest Microfilm Division, 2601 E. Yandell Drive, El Paso, Texas (79902), 1975. 12 Microfiches, $20.00.

Traditional Acupuncture for Today is in some ways a comprehensive work on acupuncture. Whether it is truly useful for today's practice is questionable, however. It consists almost exclusively of reproductions of traditional Chinese diagrams that have long been supplanted for Chinese and Japanese acupuncturists by modern, anatomically correct diagrams each of which emphasizes only a restricted number of acupuncture points. The old illustrations, as used in this work, show dozens of points on numerous meridians, of which one or two are emphasized for special consideration on each frame.

It is almost true, as the compiler says, that "this is one of the largest writings in the past 1,000 years on Oriental medicine adapted to daily use." Certainly it *is* one of the largest collections of illustrations, though they are almost totally devoid of written explanation except for a few summary statements in English and not very extensive legends in Chinese. What a modern Western physician is supposed to glean from this avalanche of nearly identical diagrams is difficult to fathom.

Detailed description of the origin and course of each meridian and the acupuncture points located thereon are so full of detail that it will be difficult, even impossible, for a novice to understand the details or to retain them in his memory. Apart from individual descriptions of each of the meridians, there is also a collection of charts which detail the regions of the body. The compiler evidently is not conversant with the original Chinese material he describes, since the descriptions are technical in the Western sense but far removed from the Oriental meaning. Illustrations are needlessly repetitive even though each of the many repeated figures concentrates on a different meridian and different acupuncture point.

On the whole, the work is virtually without original material and seems to be an indiscriminate compilation of all the writings that have ever been collected on acupuncture. Those who are totally unfamiliar with acupuncture in theory and practice may find an occasional passage worth studying. Others who already are familiar with acupuncture will find this a boring repetition of practically useless information. The reproduced woodcuts are poor and the legends nearly illegible, even using a good microfilm reader. Also the question arises when and where Dr. Ettl received his information, since the anesthesia points shown here for the purpose of cesarean section are entirely different from those currently used in the People's Republic of China. Moreover, it is absolutely misleading, for example, to give points for the treatment of deafness because the treatment of deafness by acupuncture is still in a highly experimental stage (*see* Feasibility of acupuncture as a treatment for sensorineural deafness in children. *The Laryngoscope* 84:2202-2217, Dec 1974).

Dr. Ettl's credentials for compiling a work on acupuncture are simply that he has attended numerous acupuncture training sessions, meetings and seminars and that he has come away from them feeling that he had learned too little for the time and the expenditure.

Evidently, the expenditure of $20 for a collection of hundreds of randomly collected illustrations on acupuncture would be modest, if it were felt that the work had any appreciable merit whatsoever. Apart from the difficulty of understanding the purpose of the illustrations, the reviewer is disturbed by the lack of identification and reference to the origin of these illustrations. No acknowledgment is made as to from where the material is "borrowed" or if it was taken with the author's or publisher's permission.

In all probability, the book has served to clarify Dr. Ettl's own understanding of acupuncture, as this could be the most valid explanation for the modus operandi of the compiler.

ILZA VEITH, PH D, D MED SCI

EDITOR'S NOTE: In October 1975 Dr. Veith was awarded the Doctor of Medical Sciences degree (Igaken Hakase) by the Juntendo University in Tokyo. The degree—the highest medical degree given in Japan—honors Dr. Veith for her "important contributions in the studies of Oriental Medicine" and was awarded following her examination by a faculty committee in defense of her thesis: "Foundations of Oriental Psychiatry."

* * *

IS IT WELL WITH THE CHILD?—A Parent's Guide to Raising a Mentally Handicapped Child—Susan Strauss. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1975. 152 pages, $7.95.

This is another mother's account of a retarded child. She relates with clarity her mounting concern over a child who is different and her frustrations in obtaining examinations, counseling, and special schools.

She describes her son's failure to thrive as an infant, his evaluation in a hospital at the age of five months, followed by a gradual awareness of his slow developmental progress. At four years of age, the parents indicated their anxiety to the child's pediatrician, who then referred him to a pediatric neurologist, who reportetd negative findings and offered no diagnosis. An evaluation by a psychologist resulted in referral to a psychiatrist who noted autistic features in the child's behavior. While the parents were concerned about the term "autistic," the definite diagnosis and plan for treatment elicited a period of optimism mixed with hopelessness and confusion, but they continued to worry, express concern, and grope for signs of minor improvement. Eventually, the child was placed in a residential facility on recommendation of the psychiatrist who felt that to keep him at home was to the child's disadvantage.

The author expresses concern as to why an earlier evaluation was not suggested. She wonders when a pediatrician is justified in suggesting further evaluation or counseling for a suspected developmental problem even though this might alarm the parents, perhaps unnecessarily.

This book is informative as to how one parent met the challenge of a child who is different. It also includes suggestions for locating resources for diagnosis and treatment for a child who is functioning in a subnormal manner intellectually and lists major agencies in the United States and England which are concerned with the retarded, the autistic, and the child with a learning disability.

PETER COHEN, MD

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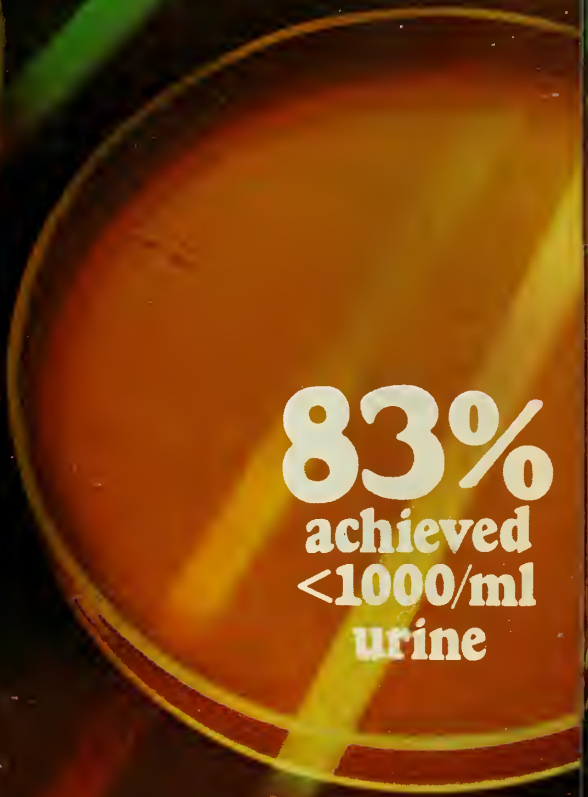

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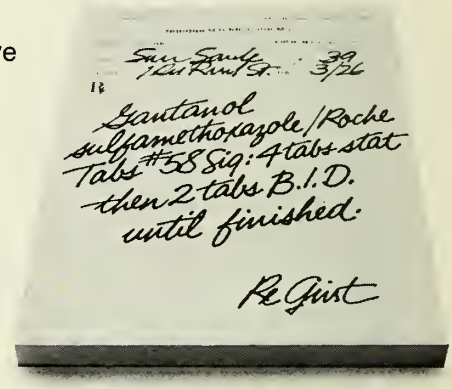

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Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

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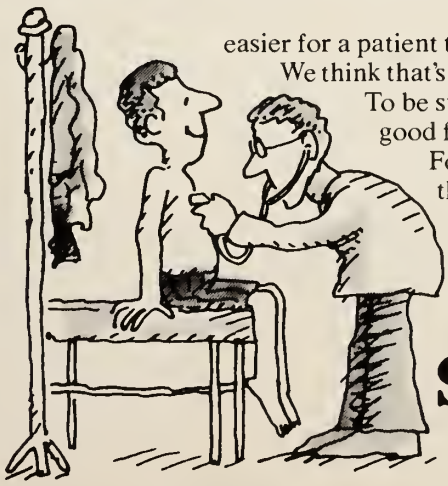

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ERLE E. PEACOCK, MD — **JULY 17-18**

Professor of Surgery, University of Arizona

Modern Surgical Practice for Family Physicians

(Intensive Instruction in Diagnosis and Surgical Technique)

ZYGMUNT PIOTROWSKI, PhD — **JULY 24-25**

Professor Emeritus of Psychology, Jefferson Medical College

Diagnosis and Prognosis of Depression and Anxiety

MATTHEW BLOCK, PhD, MD — **JULY 31-AUGUST 1**

Professor of Medicine, University of Colorado

Blood Diseases: Current Practice

JOSEPH FINNEY, PhD, MD — **AUGUST 7-8**

Professor of Education, University of Kentucky

Modern Diagnosis of Emotional Conditions

By Interview, Tests, and Computer. (To assess risks of addiction, suicide, etc. and likelihood that bodily complaints are psychological.)

GEORGE DE VOS, PhD — **AUGUST 14-15**

Professor of Anthropology, University of California, Berkeley

Diagnosis Across Racial-Cultural Bounds

(Including His Testimony in the Sirhan Case)

ALBERT ELLIS, PhD — **OCTOBER 11-12**

Institute for Advanced Study in Rational Psychotherapy, New York.

Given in San Francisco. Holiday Inn 750 Kearney Street

Rational Sex Therapy

First Day: Brief Successful Rational Counseling of Medical Patients

Second Day: Techniques of Sex Therapy; Ethics of Sex Therapy

RALPH SLOVENKO, PhD, LLB — **date not set**

Professor of Law and Psychiatry, Wayne State University

Mental Health and The Law

ANYONE ATTENDING ANY COURSE IS WELCOME TO BRING CLINICAL CASE MATERIALS FOR DISCUSSION

Fees: Two-day course $100. Either day alone $60. Six hours/day. Twenty percent reduction to interns and residents and to persons with less than a doctoral degree.

Dr. Piotrowski will also give two five-day courses in Los Angeles for Psychiatrists. July 19-23 Scientific Rorschach Testing. July 26-30 A Scientific System of Dream Analysis. Fee $200 for either course, $350 for both.

AIHS will receive proposals from nationally-known physicians and related professionals who would like to give other courses.

(WJM)

TO: AIHS Registrar, 2021 Grismer #14, Burbank, CA 91504

Enclosed is a check for my fee. Please enroll me in the course

given by _____ on (dates) _____

Name _____ MD or other degree _____

Address _____

City/State _____ Telephone _____

CONTINUING MEDICAL EDUCATION

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COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: For a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education, please write to the above address.

CANCER

June 21-25—**Head and Neck Oncology.** UCLA. Monday-Friday.

July 30-31—**Cancer Patient Counseling: Professional Case Conference.** UC Extension, Santa Cruz, at Lucille Nixon Elementary School, Palo Alto. Friday-Saturday. $50. Contact: Univ. of Calif. Extension, Santa Cruz 95064. (408) 429-2461.

MEDICINE

June 18—**Allergy for the Busy Office Practice.** PMC. Friday.

June 18-19—**The Brain and the Endocrine System.** Memorial Hospital Medical Center, Long Beach. Friday-Saturday. $175. Contact: Margaret Frederick, Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801.

June 23-25—**The Endocrine Society—58th Annual Meeting.** Hilton Hotel, San Francisco. Wednesday-Friday. Contact: The Endocrine Society Annual Meeting Office, 9650 Rockville Pike, Bethesda, Md. 20014.

June 29-July 2—**Interpretative Enzymology.** UCSD. Tuesday-Friday.

July 12-15—**2nd International Symposium on Psoriasis.** STAN. Monday-Thursday.

July 31-August 1—**Blood Diseases: Current Practice.** American Institute for Higher Studies at Holiday Inn, Hollywood. Saturday-Sunday. $100; $60, one day. Contact: AIHS Registrar, 2021 Grismer, #14, Burbank 91504.

August 3—**Seminars in Nephrology.** USC. Tuesday.

August 25-27—**Cardiology Today: For the Physician in Clinical Practice.** Mt. Zion Hospital and Medical Center, Univ. of Pittsburgh School of Medicine, under auspices of the Council on Clinical Cardiology of American Heart Assn., at St. Francis Hotel, San Francisco. Wednesday-Friday. Contact: Cont. Education, Mt. Zion Hospital & Medical Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2401.

August 29-September 4—**In-Depth Nephrology Board Review Course.** Cedars-Sinai Medical Center at Beverly Hilton Hotel, Los Angeles. One week. 60 hrs. $300. Contact: Andrew Lewin, MD, Renal Hypertension, Cedars-Sinai Medical Center, P.O. Box 48750, Los Angeles 90048. (213) 855-4671.

September 11—**EKG Workshop.** PMC at Miyako Hotel, San Francisco. Saturday. $70

September 12-16—**American Academy for Cerebral Palsy.** Century Plaza Hotel, Los Angeles. Sunday-Thursday. 18 hrs. $85. Contact: James Bryan, Exec. Sec., AACP, 1255 New Hampshire Ave. NW, Suite 1030, Washington, D.C. 20036. (202) 659-8251.

September 15-17—**Clinical Allergy for the Office Practitioner—International Symposium.** PMC at Rickey's Hyatt House, Palo Alto. Wednesday-Friday. $25.

September 17-18—**Neurology for the Non-Neurologist: Common Problems of Neurology for the Internist and Family Practitioner.** Mt. Zion Hospital and Medical Center, San Francisco. Friday-Saturday. 11½ hrs. Contact: Ann Raisbeck, Dept. of Cont. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2401.

September 18-19—**Gastroenterology.** UCLA. Saturday-Sunday.

September 29-30—**American Heart Association, Greater Los Angeles Affiliate—44th Annual Fall Symposium and 9th Annual Griffith Lecture.** Hilton Hotel, Los Angeles. Wednesday-Thursday; 12 hrs. $60 for member of any heart assn.; $80, nonmember. Contact: LaVerna Titus, AHA, Greater L.A. Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

September 29-October 1—**San Francisco Heart Association—46th Annual Symposium.** Masonic Auditorium, San Fran-

(Continued on Page 37)

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

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- Caesar's Palace
- Hotel Reservations
- Preliminary Program
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JOIN US IN LAS VEGAS IN DECEMBER!

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cisco. Wednesday-Friday. Contact: S.F. Heart Assn., 259 Geary St., San Francisco 94102. (415) 982-5753.

OBSTETRICS AND GYNECOLOGY

June 15-18—**California Association for Maternal and Child Health—Annual Congress.** Royal Inn at the Wharf, San Diego. Tuesday-Friday. $15 for members; $40, nonmembers. Contact: Calif. Assn. for Maternal and Child Health, 1053 Colorado Blvd., Suite D, Los Angeles 90041. (213) 256-3117.

July 17-19—**Basic Laparoscopy: Current Principles and Practice.** UCSD at Sea Lodge, La Jolla. Saturday-Monday.

September 9-12—**Neonatology.** UCSD at Town and Country Convention Center, San Diego. Thursday-Sunday. Contact: Louis Gluck, MD, C-019 Biology Bldg., UCSD. (714) 452-4424.

September 13-15—**Medical Complications in Obstetrics and Gynecology—Annual Fall Symposium.** UCSF at Hyatt on Union Square, San Francisco. Monday-Wednesday.

September 16-18—**Workshops in (1) High Risk Pregnancy and (2) Infertility.** UCSF at Royal Lahaina Hotel, Maui, Hawaii. Thursday-Saturday.

PEDIATRICS

September 22-23—**Brennemann Memorial Lectures—33rd Annual.** Los Angeles Pediatric Society at Sportsmen's Lodge, North Hollywood. Wednesday-Thursday. Contact: Gene Black, LAPS, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

PSYCHIATRY

June 18-19—**Clinical Biofeedback in Medicine: Psychiatry and Pyschology.** UCD at Claremont Inn, Berkeley. Friday-Saturday.

June 19-20—**Advanced Psychotherapeutic Techniques.** UCLA. Saturday-Sunday.

June 23—**The Suicidal Patient: Recognition and Evaluation.** See Of Interest To All, June 23.

July 24-25—**Biofeedback Workshop for Professionals.** UC, Santa Cruz. Saturday-Sunday. Contact: Univ. of Calif. Extension, Santa Cruz 95064. (408) 429-2461.

July 24-25—**Diagnosis and Prognosis of Depression and Anxiety.** American Institute for Higher Studies at Holiday Inn, Hollywood. Saturday-Sunday. $100; $60, one day. Contact: AIHS Registrar, 2021 Grismer, #14, Burbank 91504.

August 7-8—**Diagnosis of Emotional Conditions by Interview, Tests and Computer.** American Institute for Higher Studies at Holiday Inn, Hollywood. Saturday-Sunday. $100; $60, one day. Contact: AIHS Registrar, 2021 Grismer, #14, Burbank 91504.

RADIOLOGY AND PATHOLOGY

June 20-26—**Pathology of the Lung.** UCSD. One week.

August 1-7—**American Institute of Ultrasound in Medicine.** Hyatt Regency, San Francisco. One week. Contact: Ms. D. LaMaster, Exec. Sec., P.O. Box 25606, Oklahoma City 73125.

September 18—**Radiology Symposium.** Southern Calif. Permanente Medical Group at Beverly Hilton Hotel, Los Angeles. Saturday. Contact: Shirley Gach, So. Calif. Permanente Med. Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

SURGERY AND ANESTHESIOLOGY

June 24-25—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

June 26—**Clinical Conference in Ophthalmology.** STAN. Saturday. 7 hrs. $35.

July 14-18—**Modern Surgical Practice for Family Physicians.** American Institute for Higher Studies at Holiday Inn, Hollywood. Wednesday-Sunday. $100; $60, one day. Contact: AIHS Registrar, 2021 Grismer, #14, Burbank 91505.

July 15-16—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

(Continued on Page 41)

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(Continued from Page 25)

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PHYSICIANS—interested in regular hours, liberal salary and fringe benefits. Stimulating medical careers in emergency and critical care medicine. Send résumé to: Wayne M. Bailey, Administrative Director, Critical Care, 724 South Edisto Ave., Columbia, SC 29205.

AAFP, 43, wants FP or GP who has already had his coronary or doesn't want to have it, to associate with me in a low-key, high quality, small town practice in the Willamette Valley of Oregon. No hospital work unless you want it. Rare house calls, no night work, no OB, no welfare. Good emergency services, good consultants in the area. Four excellent hospitals within 30 miles. Plan to work 3 days/wk or more as you desire. Good schools, 30 miles to two State Universities. Minutes to mountains and two hours to ocean. Good fishing and hunting. Recreational and family community with agricultural, cattle, timber and lumbermill base, some tourism. If interested, write Box 9462, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

SURGEONS, FAMILY PRACTICE, E.N.T., OPHTHALMOLOGIST, and INTERNAL MEDICINE PHYSICIANS should consider McCook, Nebraska as an excellent area for relocation. McCook has a new, 56-bed, accredited hospital that serves 15-20,000 people. McCook has 4 lakes within 60 miles for fishing and recreational purposes and is only 2 air hours from Denver and Omaha. For complete information, contact: Ken Noteboom, Administrator, Community Hospital, P.O. Box 310, McCook, Nebraska 69001.

PUBLIC HEALTH OFFICER: Kern County seeks highly qualified physician with administrative experience to direct County Health Department. Salary $37,051-$45,232 depending on qualifications with excellent management benefits. For information contact: Kern County Personnel Department, 1120 Golden State Ave., Bakersfield, CA 93301; (805) 861-2195.

RESIDENCY IN EMERGENCY MEDICINE beginning July 1976. Two-year program, prerequisite one year post-graduate training. Busy Emergency Department in university affiliated teaching hospital. Send résumé and three letters of recommendation (or names of three references) to: William G. Malette, MD, Kern Medical Center, 1830 Flower St., Bakersfield, CA 93305. Telephone: (805) 323-7651, extension 346.

MEDICAL OR CLINICAL DIRECTOR—for non-profit, tax exempt abortion clinic. To supervise, train, research, relate to community, institute new programs. Salary $40,000 to $60,000. Contact: Ms. Carolyn Buhl, Director, PRETERM, 10900 Carnegie Ave., Cleveland, Ohio 44106; Phone (216) 368-1006.

GENERAL INTERNIST and CARDIOLOGIST INTERNIST needed to join multispecialty group of 35 doctors in San Diego, California. Reply with curriculum vitae to Box 9463, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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FACULTY FOR EMERGENCY MEDICINE RESIDENCY PROGRAM beginning July 1976, university affiliated teaching hospital. Board Certified in Surgery, Internal Medicine or recent graduate-approved residency in Emergency Medicine. Salary competitive; malpractice insurance paid. California license necessary. Send curriculum vitae and names of three references to: William G. Malette, MD, Kern Medical Center, 1830 Flower Street, Bakersfield, CA 93305. Telephone: (805) 323-7651, extension 346.

CALIFORNIA—UNIVERSITY AFFILIATED PEDIATRICS RESIDENCY. Unexpected opening for Pediatrics Resident in University of California, San Francisco affiliated teaching hospital. Excellent supervision by a strong full-time staff. Must be eligible for California license or have FLEX. Competitive salary. Close to National Parks. For information write or phone James McKenna, MD, Valley Medical Center, 445 S. Cedar, Fresno, CA 93702, (209) 251-4833, ext. 2321.

INTERNIST-OB-GYN outstanding opportunity with 16-man multi-specialty corporate group located ideally between Chicago and Milwaukee on the shores of Lake Michigan. Modern well equipped facilities in a progressive community. Excellent income, congenial working conditions, full corporate membership within one year. Please send curriculum vitae to: Stan Englander, MD, Kurten Medical Group, S.C., 2405 Northwestern Ave., Racine, Wis. 53404; Tel.: (414) 632-7521.

ORTHOPEDIC SURGEON (ACADEMIC), to establish a teaching service in a university affiliated VA Hospital. Board certification in orthopedic surgery necessary. Send curriculum vitae and references to Veterans Administration Hospital; 510 E. Stoner; Shreveport, LA 71130.

ACTIVE GP GROUP in San Joaquin Valley needs another GP as replacement for retiring doctor. Good income, good hospital facilities, excellent living conditions and recreational facilities. Practice includes Obstetrics, Surgery, Internal Medicine, and Pediatrics. Box No. 9465, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

SEEKING BOARD CERTIFIED OR QUALIFIED INTERNIST, preferably with subspecialty in allergy or gastroenterology, to associate with two established internists with subspecialities in cardiology and pulmonary diseases. New office building and facilities with unlimited land available for expansion across from a major hospital. Rapidly growing county seat-university-community college town on central coast of California; population 40,000 with 150,000 in area and several State institutions. Financial arrangements open and negotiable, eventual partnership desired. Completely equipped office includes lab, x-ray. Excellent fringe benefits and supporting staff. Beautiful multifaceted recreational and geographic area; good schools and churches. Send curriculum vitae to Box Number 9471, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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COLLABORATOR WANTED

PROFESSIONAL MEDICAL WRITER, EXPERIENCED, would like to team up with a physician to write a popular medical column for newspaper or magazine; terms of collaboration to be worked out. Box No. 9464, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

OFFICES TO LEASE OR RENT

MEDICAL SUITES AVAILABLE—Foothill Medical Building, 21297 Foothill Blvd., Hayward, Calif. One 850 sq. ft. and one 760 sq. ft. Each has a doctor's office, nurse's station, waiting room, and three treatment rooms. The building has an X-ray, medical laboratory, and a pharmacy. It is ideal for a general practitioner or an internist. Some free rent. For information call (415) 582-6942.

WEST LOS ANGELES PRIME MEDICAL SPACE—Wilshire West Medical Plaza, located 11645 Wilshire Blvd., ¼ mile west of San Diego Fwy. Ultra modern, full security, heliport, exceptional parking. City and ocean views. Choice spaces still available. The 11-story medical bldg. is scheduled for completion fall 1976. Leases have been signed for clinical and radiological labs, pharmacy and restaurant. Suite sizes to suit. Call Barbara Perlman or Chuck Wright, Coldwell Banker Co.; (213) 274-6811.

FOR RENT: The newest and largest professional building in the South San Diego community of Imperial Beach, suites available can be customized to suit tenant. This is excellent opportunity for pediatrics, gynecology, dermatology, ophthalmology, general surgery, general practice, internal medicine and psychiatry. Photos and particulars available upon request from John E. Geis, DDS, 1340 Coronado Ave., Suite 201, Imperial Beach, CA 92032; office (714) 424-3931.

LOCUM TENENS

CARDIOLOGY LOCUM TENENS. Want Board certified or qualified Cardiologist for July or August, 1976. A. J. Calciano, MD, 3141 Paul Sweet Road, Santa Cruz, CA 95065; phone: (408) 476-6200.

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SIEMENS PORTABLE 8 CHANNEL EEG MACHINE for sale. (415) 939-9400; Mon thru Fri, 10-5.

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FOR LEASE: Large office ideal for small group located in Lawndale, California. Near Hawthorne Community Hospital and Gardena Memorial. Contact **Allen Hooper, MD, 1200 N. State St. P.O. Box 313, Los Angeles, CA 90033; Phone (213) 226-6675.**

(Continued from Page 37)

August 1-8—**International College of Surgeons—3rd Annual Hawaii Meeting.** Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $100. Contact: William A. Houser, Admin. Dir., ICS, 1516 N. Lake Shore Dr., Chicago 60610. (312) 642-3555, ext. 61.

August 1-13—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. 100 hrs. $1,200 for otolaryngologists; $900, residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

August 5-6—**Keratoplasty.** PMC at Stanford Court Hotel, San Francisco. Thursday-Friday. $175.

August 6-7—**Intraocular Lens Implantation.** Santa Monica Hospital Medical Center, Santa Monica. Friday-Saturday. 16 hrs. $600. Contact: Jeanne Harris, Charlie Ruggles Ophthalmology Dept., Santa Monica Hospital Medical Center, 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

August 7-14—**Diagnosis and Management of Corneal and External Disease Problems.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

August 12-13—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

August 15-18—**Urology.** UCLA at Lake Arrowhead. Sunday-Wednesday.

September 10-11—**Trauma.** UCSF at Mary's Help Hospital, Daly City. Friday-Saturday.

September 11-18—**Practical Management of Anesthetic Problems—2nd Annual Symposium.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

September 15-16—**Strabismus.** PMC at Stanford Court Hotel, San Francisco. Wednesday-Thursday. $175.

September 16-17—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

June 18-19—**The Brain and the Endocrine System.** See Medicine, June 18-19.

June 23—**The Suicidal Patient: Recognition and Evaluation.** PMC. Wednesday. $50.

June 23-25—**Clinical Pharmacology—Rational Basis of Therapeutics.** American College of Physicians at UCSF. Wednesday-Friday. Contact: Registrar, Postgraduate Courses, ACP, 4200 Pine St., Philadelphia, PA 19104.

July 10, 17—**Wound Management.** UCSD. Two Saturdays.

July 12-16—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Town and Country Hotel, San Diego. Monday-Friday.

July 14-18—**Modern Surgical Practice for Family Physicians.** See Surgery, July 14-18.

August 2-6—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday.

August 14-25—**Postgraduate Refresher Course—19th Annual.** USC, Univ. of Hawaii School of Medicine, Tripler General Hospital at Honolulu and Maui or Kauai, Hawaii. 12 days.

August 18-22—**Family Practice Refresher Course—3rd Annual.** UCLA. Wednesday-Sunday.

August 22-27—**Family Practice Refresher Course.** UCD at Del Monte Hyatt, Monterey. Sunday-Friday.

August 23-27—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD. Monday-Friday.

August 28-September 4—**Family Practice Refresher Course—7th Annual.** UCI at South Coast Plaza Hotel, Costa Mesa. One week. 46 hrs. $225. Contact: J. Blair Pace, MD, 101 City Dr. So., Orange 92668. (714) 634-5171.

August 29-September 2—**Autogenic Training.** UCLA at Asilomar. Sunday-Thursday.

August 29-September 6—**Pharmacology.** UCSF at Maui, Hawaii. Nine days.

August 31-October 19—**Evening Lectures in Medicine.** UCSF at Oakland Hospital, Oakland. Tuesday evenings.

September 17-18—**Neurology for the Non-Neurologist: Common Problems of Neurology for the Internist and Family Practitioner.** See Medicine, September 17-18.

September 20-24—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Hilton Hotel, San Diego. Monday-Friday.

September 20-24—**Topics in Emergency Medicine—Basic Course.** UCSF at Franklin Hospital, San Francisco. Monday-Friday.

Audio-Digest Foundation. A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: Family Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $90 per year. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90057. (213) 483-3451.

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Providence Medical Center, 700 NE 47th Avenue, Portland

97213. Contact: Dave Gilbert, MD, Providence Medical Center:

Every Wednesday, 8:00 a.m. to 9:00 a.m.—**Spring Medical Grand Rounds.**

University of Oregon Medical School, Family Practice Center, 3181 S.W. Sam Jackson Park Road, Portland 97201:

Every Thursday. 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School.

FAMILY PRACTICE

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Family Practice Center, University of Oregon Medical School, Portland. Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

June 24—**Family Practice Education Program.** Woodland Park Hospital Auditorium. Contact: Raymond Reichle, MD, Woodland Park Hospital, Department of Family Practice, 10300 N.E. Hancock Street, Portland 97220.

August 4-6—**Woodland Park Hospital Family Practice Symposium on Immunology.** Gearhart by the Sea, Gearhart, Oregon. Contact: R. T. Gustafson, MD, Woodland Park Hospital, Department of Family Practice, 10300 N.E. Hancock Street, Portland 97220.

SURGERY

September 6-7—**Western Orthopedic Society Annual Meeting.** Sunriver Lodge, Bend. Contact: Stanley E. Donahoo, MD, 1819 West Harvard Blvd., Roseburg 97470.

OF INTEREST TO ALL PHYSICIANS

September 22-24—**Oregon Medical Association Annual Scientific Session.** Hilton Hotel, Portland. Contact: Sondra Gleason, Oregon Medical Association, 2164 S.W. Park Place, Portland 97205.

WASHINGTON, MONTANA, ALASKA and IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

June 14-17—**Disorders of Red Cell Proliferation.** (ACP). Sunday-Thursday. Rosario Resort, Orcas Island, WA. Hours to be determined. ASH, ACP members, fellows, residents, $140; non-members, $195; associates, $70. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

June 17-19—**Behavioral Methods in Medical Practice.** Thursday-Saturday. University Tower Hotel, Seattle. 8 hrs, $60. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

June 25—**Bicentennial History of Medicine in the United States.** Friday. Kane Hall, Univ. of Wash., Seattle. 6½ hrs. $75. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

July 26-29—**World of the Heart and Lung: America's Hearts and Lungs After 200 Years.** Monday-Thursday. University Tower Hotel, Seattle. 24½ hrs. $155. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-67, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

August 3-6—**American Academy of Clinical Toxicology and American Association of Poison Control Centers Joint Meeting.** Tuesday-Friday. Olympic Hotel, Seattle. Hours to be determined. Members, $50; non-members, $75; interns, residents, allied health personnel, $10. Contact: Barry H. Rumack, MD, Rocky Mountain Poison Control Center, West 8th and Cherokee St., Denver, CO 80204.

September 10-11—**University of Washington School of Medicine Alumni Days.** Friday-Saturday. Univ. of Wash. Sch. of Med., Seattle. Contact: John N. Lein, MD, Dir. CME, E-303 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495.

September 10-13—**Washington State Medical Association Annual Meeting.** Friday-Monday. Olympic Hotel, Seattle. Contact: Harlan R. Knudson, Exec. Dir., 444 N.E. Ravenna Blvd., Seattle 98115. (206) 523-9110 or 1-800-552-0602.

September 17-18—**Medical Genetics.** Friday-Saturday. Child Development and Mental Retardation Center, Univ. of Wash., Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

September 23-24—**Ophthalmology and Otolaryngology for Primary Physicians.** Thursday-Friday. Seattle. Location, hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

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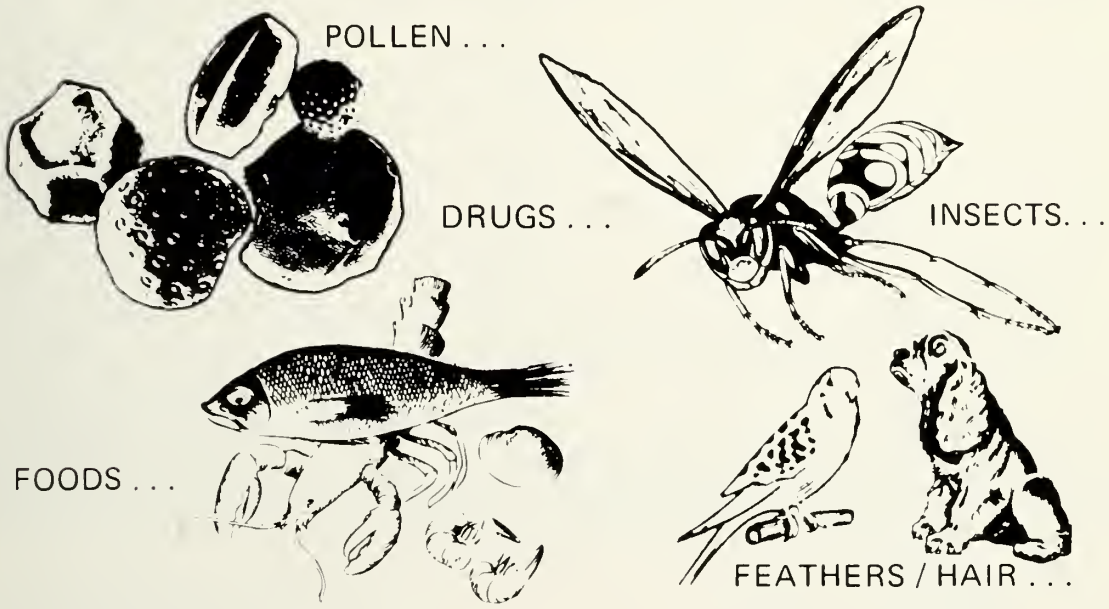

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The Journal of Allergy and Clinical Immunology
Vol. 49, No. 1-9, 1972

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Lancet 2:1105, 1967

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An In Vitro Test as used in the detection of immediate hypersensitivity in man.
V Latin American Congress of Allergy and Immunology National Academy of Medicine
Buenos Aires, Argentina, October 1974

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